NDA 22-231
Terlipressin for the Treatment of HRS Type 1

Cardiovascular and Renal Drugs Advisory Committee

July 15, 2020

Introduction


Khurram Jamil, MD

Khurram Jamil, MD

Vice President, Clinical Research in Hepatology
Critical Care Division
Mallinckrodt

Hepatorenal Syndrome Type 1 (HRS-1)

- **Rare condition: estimated US incidence ~ 35,000**
- **Functional renal failure with structurally normal kidney**
  - Portal hypertension leads to splanchnic vasodilation
  - Compensatory renal vasoconstriction
- **Occurs in the setting of decompensated cirrhosis**
  - Primary etiologies: NASH, hepatitis C or alcoholic liver disease

NASH: Non-Alcoholic Steato-Hepatitis

Diagnosis of HRS-1

- **Diagnosis of exclusion**
- **Rapid intervention is critical**
- **Requires interdisciplinary approach**
  - Hepatologists
  - Nephrologists
  - Intensivists
  - Transplant surgeons

Treatment of HRS-1

- **Goals of treatment**
  - Improve renal function
  - Reverse HRS-1
- **Successful treatment**
  - Facilitates medical management of critically ill patient
  - Allows recovery of patients with reversible component of liver disease
  - Improves outcomes of patients with liver transplant
- **No approved treatment for HRS-1 in the US**

Terlipressin

- A synthetic vasopressin analogue
- V_1 receptor selectivity: splanchnic vasculature
- Restores effective blood volume and improves renal perfusion
- Improves renal function, HRS reversal, clinical outcomes
- Approved in EU, Asia, Australia, Africa and Latin America
- Recommended for use in combination with albumin[1,2]

1. Angeli P. et al. *J Hepatol*. 2015;62(4):968-74.
2. EASL Clinical Practice Guidelines. *J Hepatol*. 2018;69:406-460

Terlipressin Phase 3 Program

OT-0401 Study
N=112
Supportive

REVERSE Study
N=196
Additional Data

CONFIRM Study
N=300
Pivotal

Overview of Study Findings

- **Demonstrated efficacy**
  - Higher rate of HRS reversal and greater improvement in SCr
  - Decreased incidence of RRT
  - Decreased length of ICU stay
  - Improved outcomes in transplant patients
- **Manageable safety profile**
  - GI and ischemia events
- **CONFIRM study: higher rate of respiratory and related sepsis events**
  - Imbalance of deaths on terlipressin driven by these events
  - Risk management program should reduce events and deaths

SCr=Serum creatinine

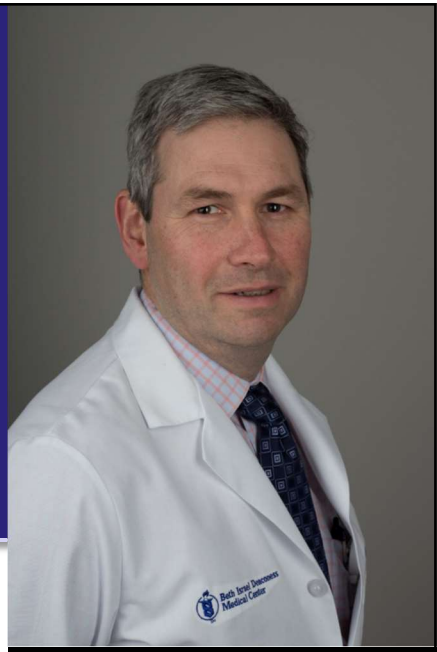
Agenda

Introduction	**Khurram Jamil, MD** Vice President, Clinical Research in Hepatology Critical Care Division, Mallinckrodt
Pathophysiology of HRS-1 and Rationale for Terlipressin	**Michael P. Curry, MD** Section Chief of Hepatology Beth Israel Deaconess Medical Center Harvard Medical School
Efficacy	**Khurram Jamil, MD** Vice President, Clinical Research in Hepatology Critical Care Division, Mallinckrodt
Safety	**Chris Pappas, MD, JD, FAASLD** Clinical Hepatologist Consultant, Mallinckrodt
Risk Management	**Khurram Jamil, MD** Vice President, Clinical Research in Hepatology Critical Care Division, Mallinckrodt
Benefit/Risk and Clinical Considerations	**Arun Sanyal, MD** Professor, Department of Internal Medicine Division of Gastroenterology, Hepatology and Nutrition Virginia Commonwealth University School of Medicine

Available for Questions

Kevin Moore, PhD, MBBS	Professor of Hepatology Ex Secretary, International Club of Ascites Royal Free Hospital, University College, London
Juan Carlos Q. Velez, MD	Chair Department of Nephrology Ochsner Clinic Foundation, New Orleans, LA
Shannon Escalante	Biostatistics, Mallinckrodt
Rick Fitch, PhD	Nonclinical, Mallinckrodt

Pathophysiology of HRS-1 and Rationale for Terlipressin



Michael P. Curry, MD

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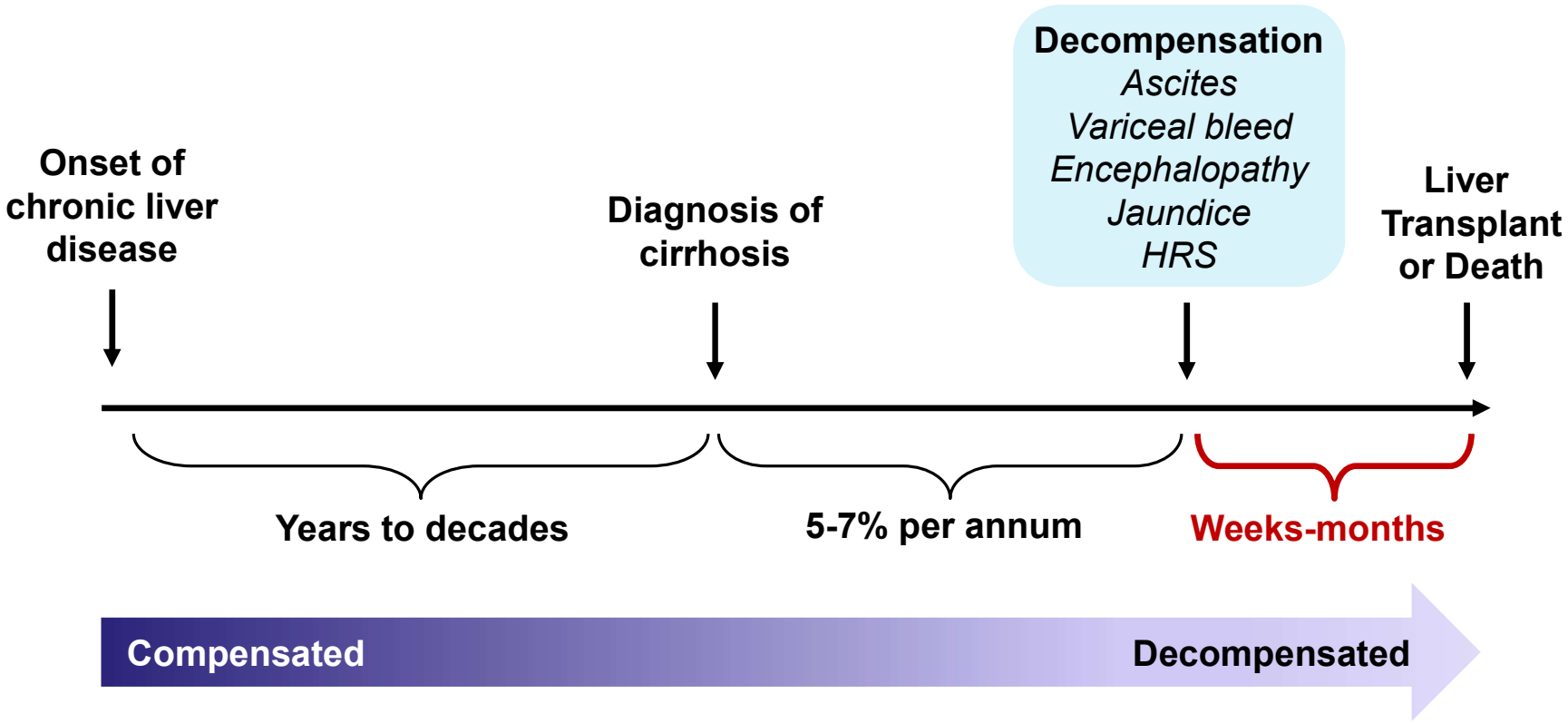
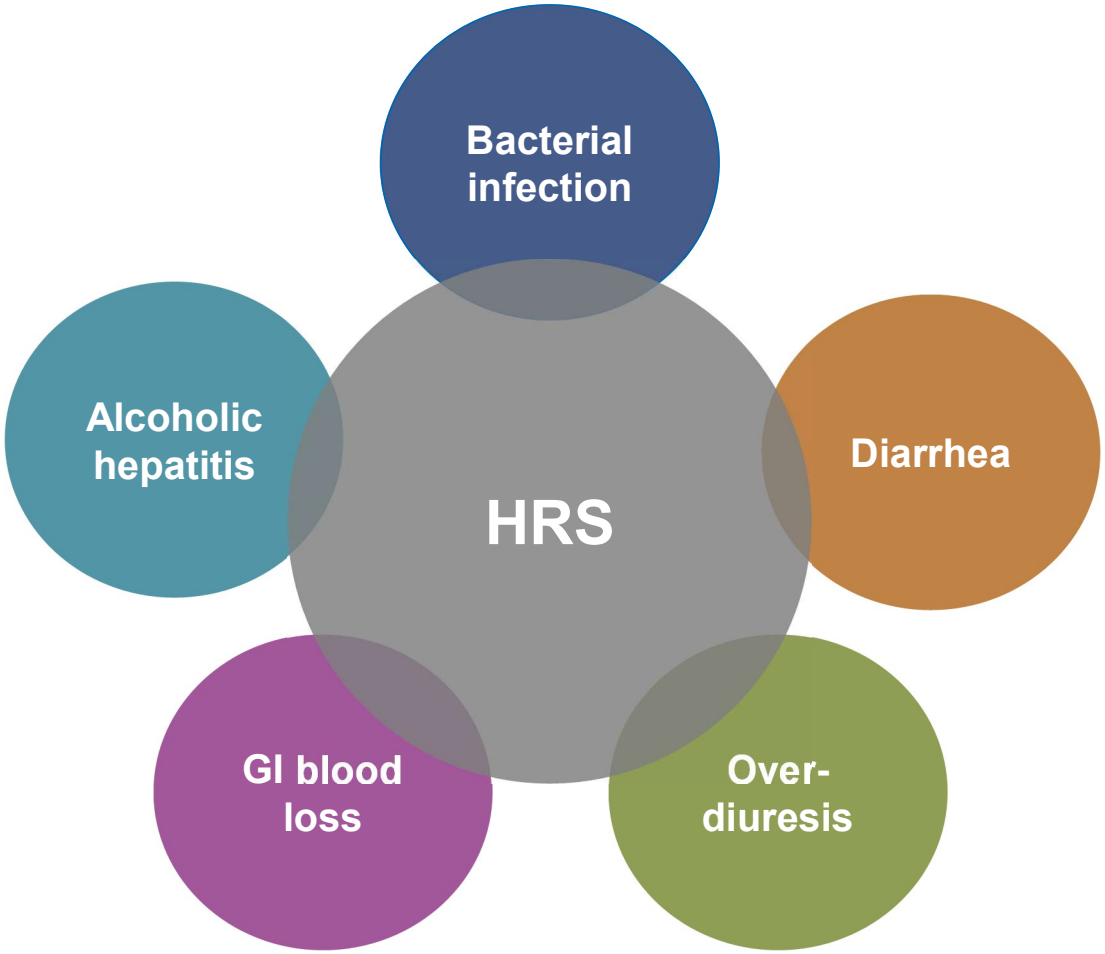
Section Chief of Hepatology
Beth Israel Deaconess Medical Center
Harvard Medical School

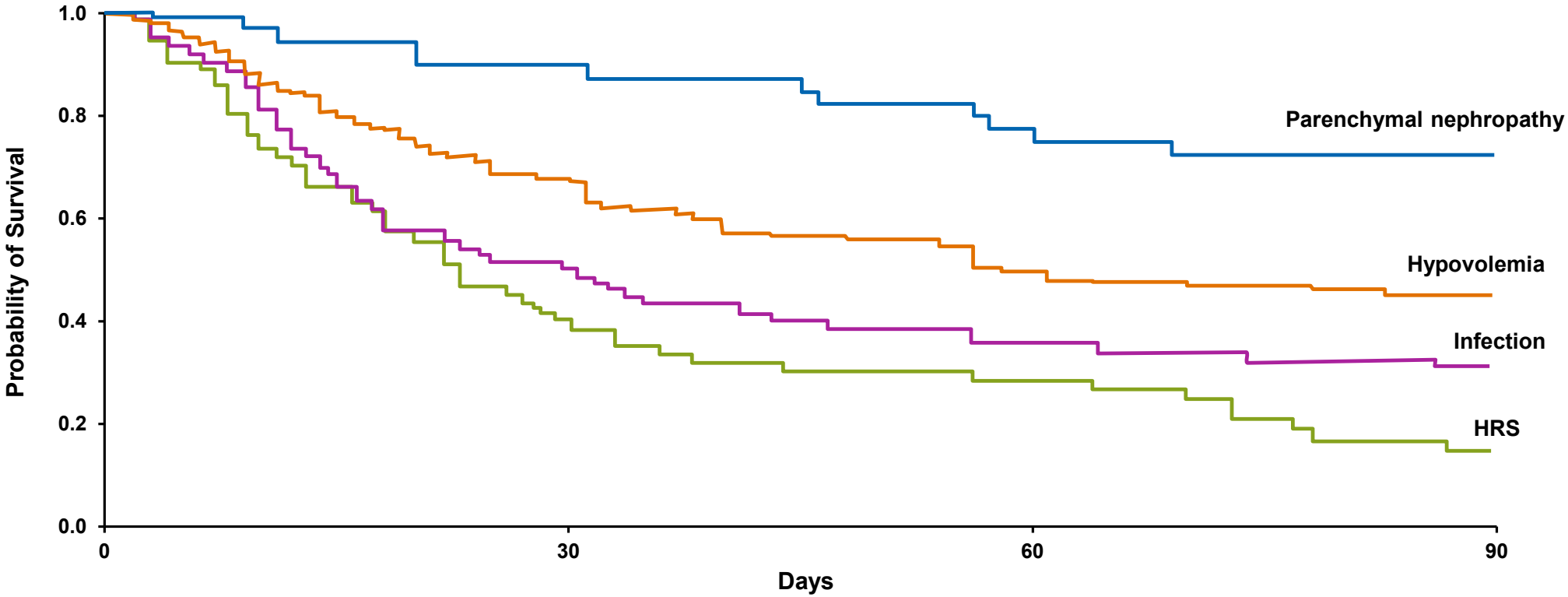
Progression of Liver Disease and Decompensation



Common Precipitating Factors of HRS



Renal Failure in Cirrhosis



Martín-Llahí et al, *Gastroenterology* 2010.

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Hepatorenal Syndrome Type 1 (HRS-1)

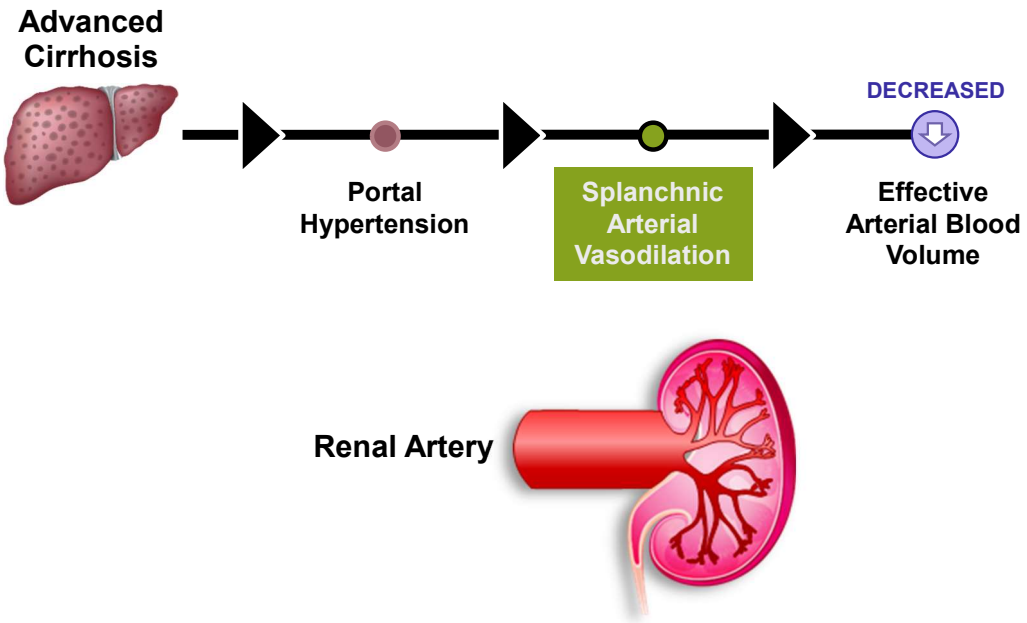
- **Serious acute complication of decompensated cirrhosis**
- **Incidence in the US is 35,000 patients per annum**
- **Potentially reversible functional renal failure**
  - Renal hypoperfusion due to hemodynamic changes
- **One aspect of complex multi-organ dysfunction**

Pant C, et al. *J Invest Med*. 2016;64(1):33-8.
Wong F. *Nat Rev Gastroenterol Hepatol*. 2012;9:382-91.

Burden of HRS-1

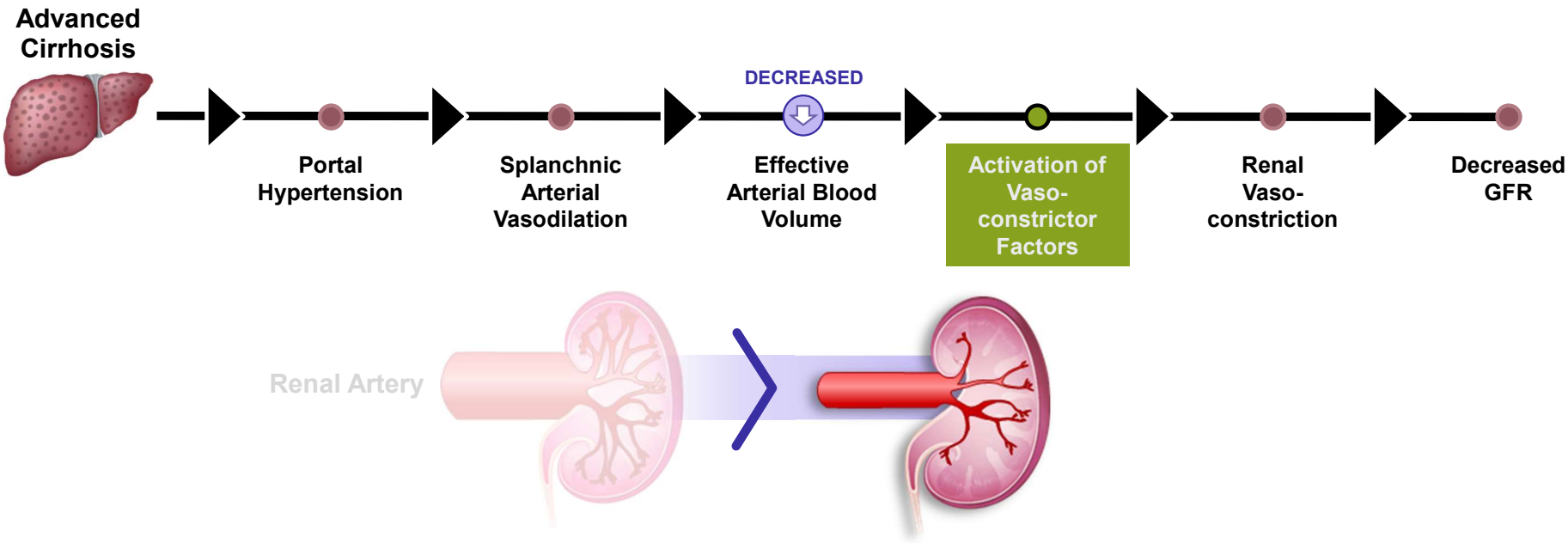
- **Patient**
  - Acute complication of a critical illness
  - Risk of transplant delisting
  - Prolonged hospitalization and increased ICU days
- **Family and caregivers**
- **Healthcare system**
- **Physicians and healthcare team**

Onset of HRS-1



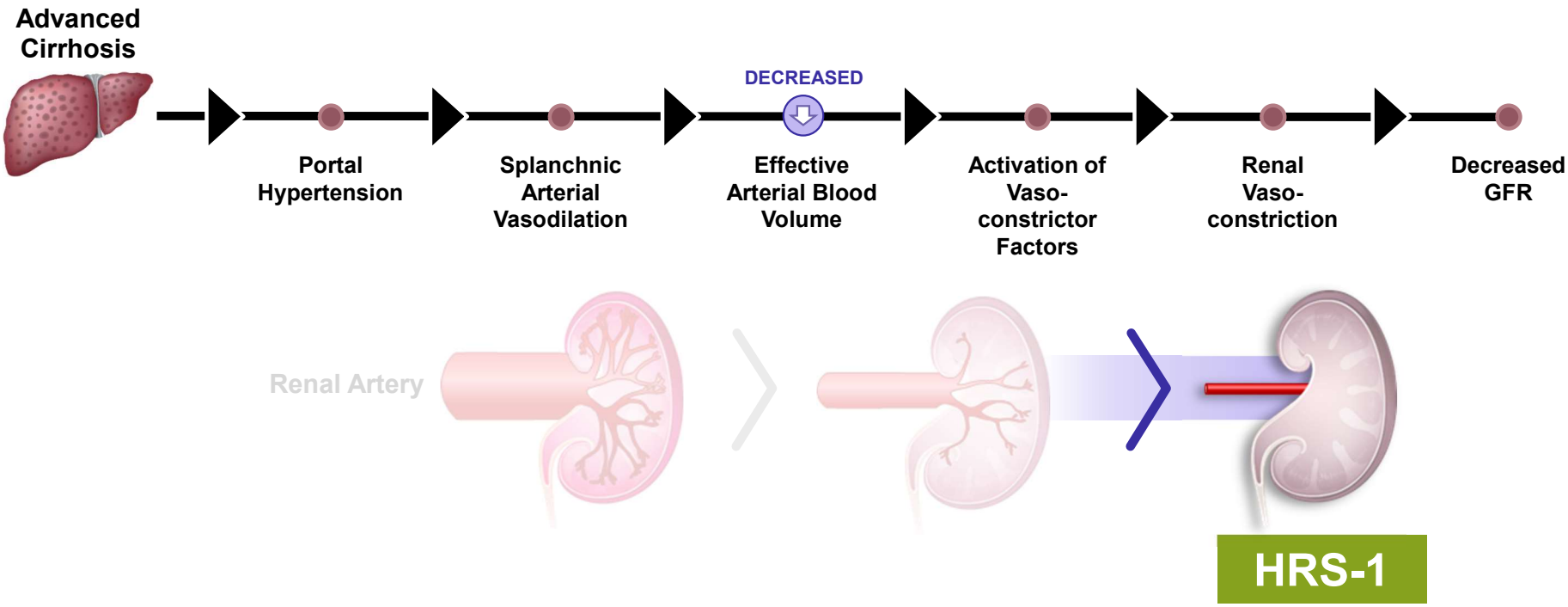
Based on Wong F. *Nat Rev Gastroenterol Hepatol*. 2012;9:382-91.

Increased Renal Vasoconstriction



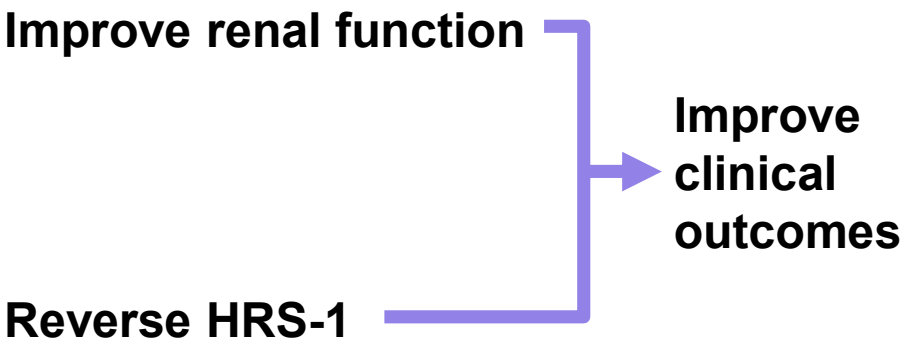
Based on Wong F. *Nat Rev Gastroenterol Hepatol*. 2012;9:382-91.

Increased Renal Vasoconstriction: HRS-1

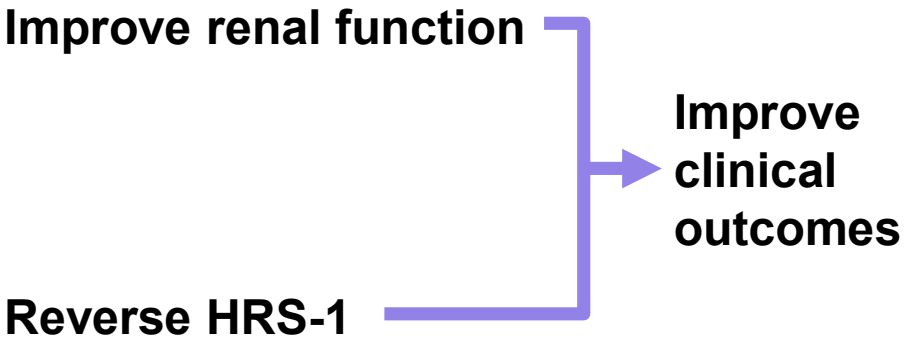


Based on Wong F. *Nat Rev Gastroenterol Hepatol*. 2012;9:382-91.

HRS-1 Treatment Desired Outcomes



HRS-1 Treatment Desired Outcomes



Less RRT
- Improve RRT-free survival

Facilitate medical management

Potential to return to compensated state

Shorter ICU stays

Liver transplanted patients
- Less RRT
- Improved survival

Liver Transplantation

- **Definitive treatment for advanced decompensated cirrhosis**
- **Not available to all patients**
  - Over 12,000 candidates are waiting for liver transplant
  - Only 8,767 liver transplants were performed in 2019
  - Over 1,000 patients died on the waiting list
  - Over 1,000 were removed from waiting list as “too sick” to transplant

European Association for the Study of the Liver (EASL). *J Hepatol*. 2018;69(2):406-60.
Organ Procurement and Transplantation Network. OPTN Policies updated 03 April 2020.
Runyon BA. AASLD. *Hepatology*. 2013;57(4):1651-3.

Ways to Treat HRS-1

- **Renal replacement therapy (RRT)**
  - Does not restore renal function
  - Does not improve prognosis
  - High risk in cirrhotic patients
- **Albumin**
  - Volume expansion
  - Anti-inflammatory
- **Vasoconstrictors**
  - Reduce vasodilation of advanced cirrhosis

Bernardi M, et al. *Critical Care*. 2012;16:211.
Garcia-Martinez R, et al. *Hepatology*. 2013 Nov;58(5):1836-46.
European Association for the Study of the Liver (EASL). *J Hepatol*. 2018;69(2):406-60.
Runyon BA. AASLD. *Hepatology*. 2013;57(4):1651-3.

Outcomes of RRT in Patients with Cirrhosis

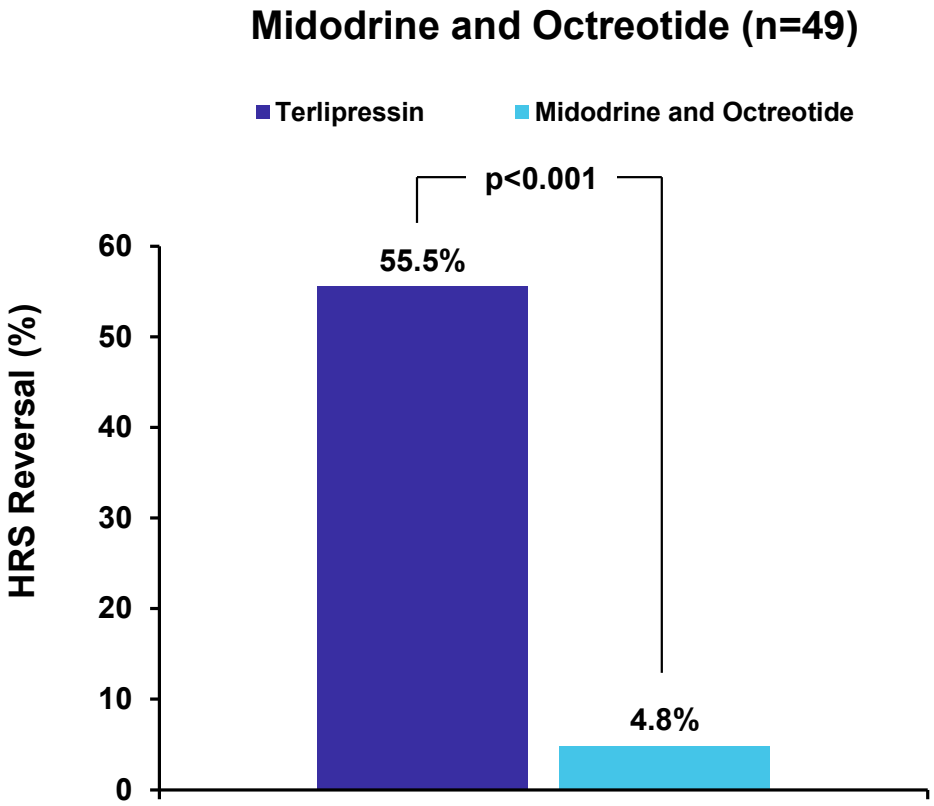
- **Study of cirrhotics admitted to ICU**
  - ~50% of patients required mechanical ventilation and vasopressors
  - ~40% of patients required RRT
    - 28 day mortality of 83%
    - Only 13% had spontaneous renal recovery after ICU discharge
- **RRT in cirrhotics is associated with greater morbidity and worse outcomes**

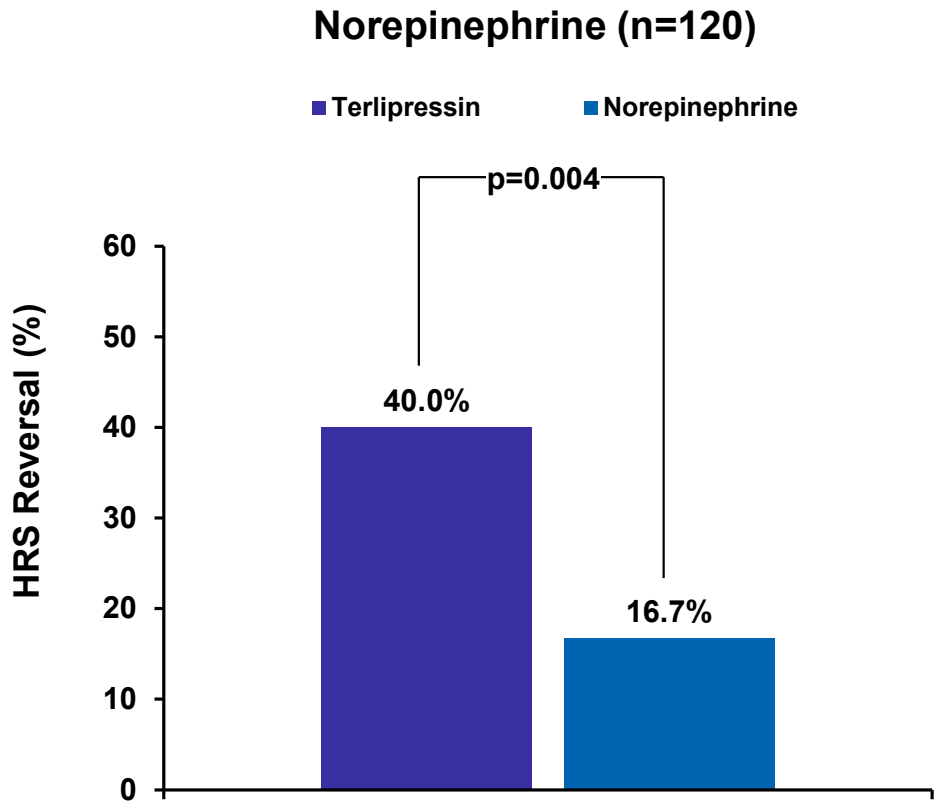
Staufer K, et al. Liver Int. 2017;37:843-850.

Vasoconstrictors Used for HRS-1

- **Terlipressin**
  - Most clinical trial evidence; not available in US
- **Midodrine and octreotide**
  - Used despite limited evidence
- **Norepinephrine**
  - Used despite limited evidence; administered in ICU setting

Vasoconstrictors Available in US vs. Terlipressin





Cavallin M, et al. *Hepatology* 2015;62:567–574
Arora V, et al. *Hepatology* 2020;71:600-610

Guidelines Referencing Terlipressin as Preferred Therapy

Consensus Recommendations of the International Club of Ascites

- Terlipressin and albumin are most investigated and effective treatment for HRS-1

European Association for the Study of the Liver (EASL) Clinical Practice Guidelines

- Terlipressin plus albumin as the first-line therapy for treatment of HRS-AKI
- Terlipressin dose: i.v. boluses of 1 mg every 4-6 hours

Angeli P, et al. *J Hepatol* 2015;62:968-74.
European Association for the Study of the Liver (EASL). *J Hepatol*. 2018;69(2):406-60.

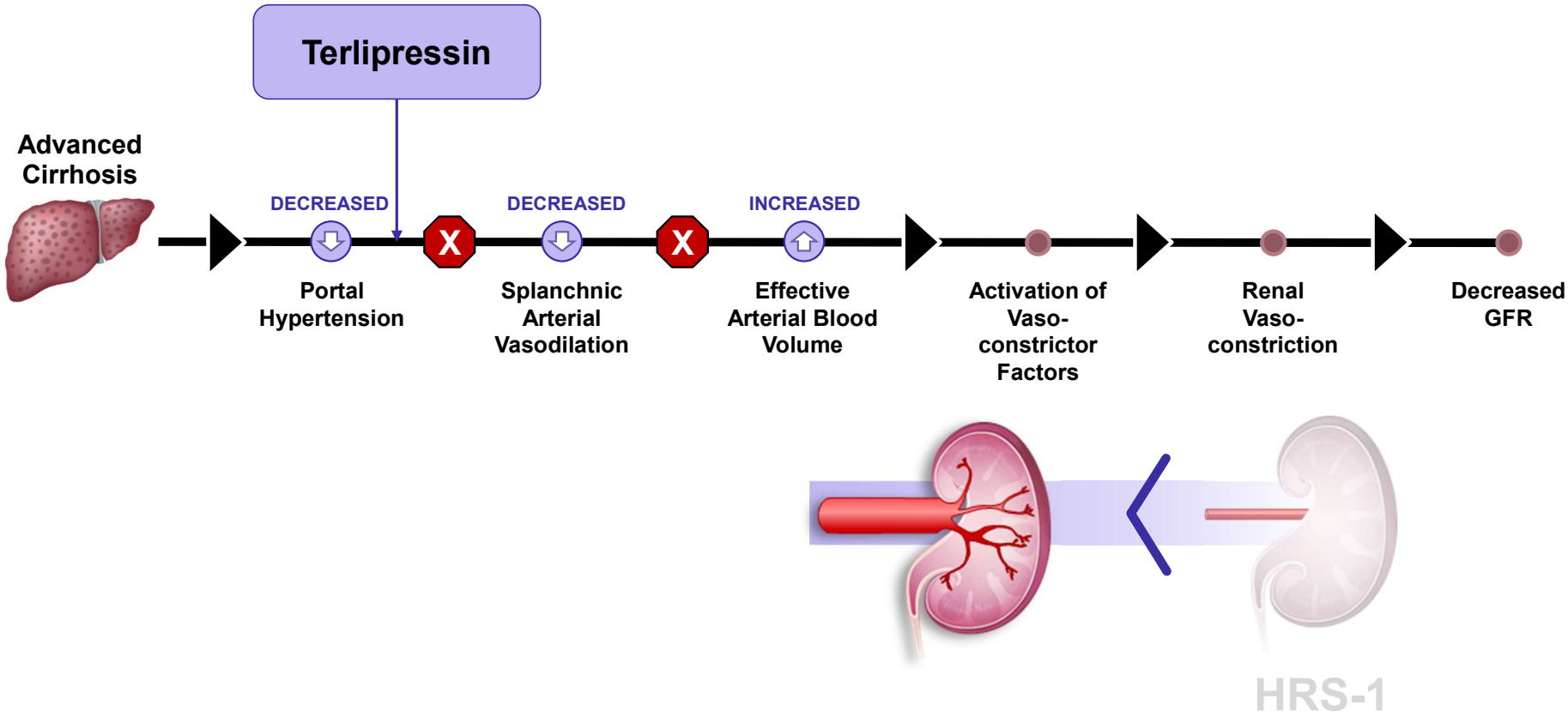
Terlipressin

- **Synthetic vasopressin analogue**
  - Prodrug for lysine-vasopressin (LVP); 1% of its V_1 activity
  - LVP slowly released via tissue peptidase metabolism
  - Slow release is advantage over vasopressin
  - $T_{½} \approx 50$ minutes (LVP $T_{½} \approx 3$ hrs)
- **Administered IV**
  - Typical treatment period is 6 days (up to 14 days)

Terlipressin – V1 Dominant Effects in HRS-1

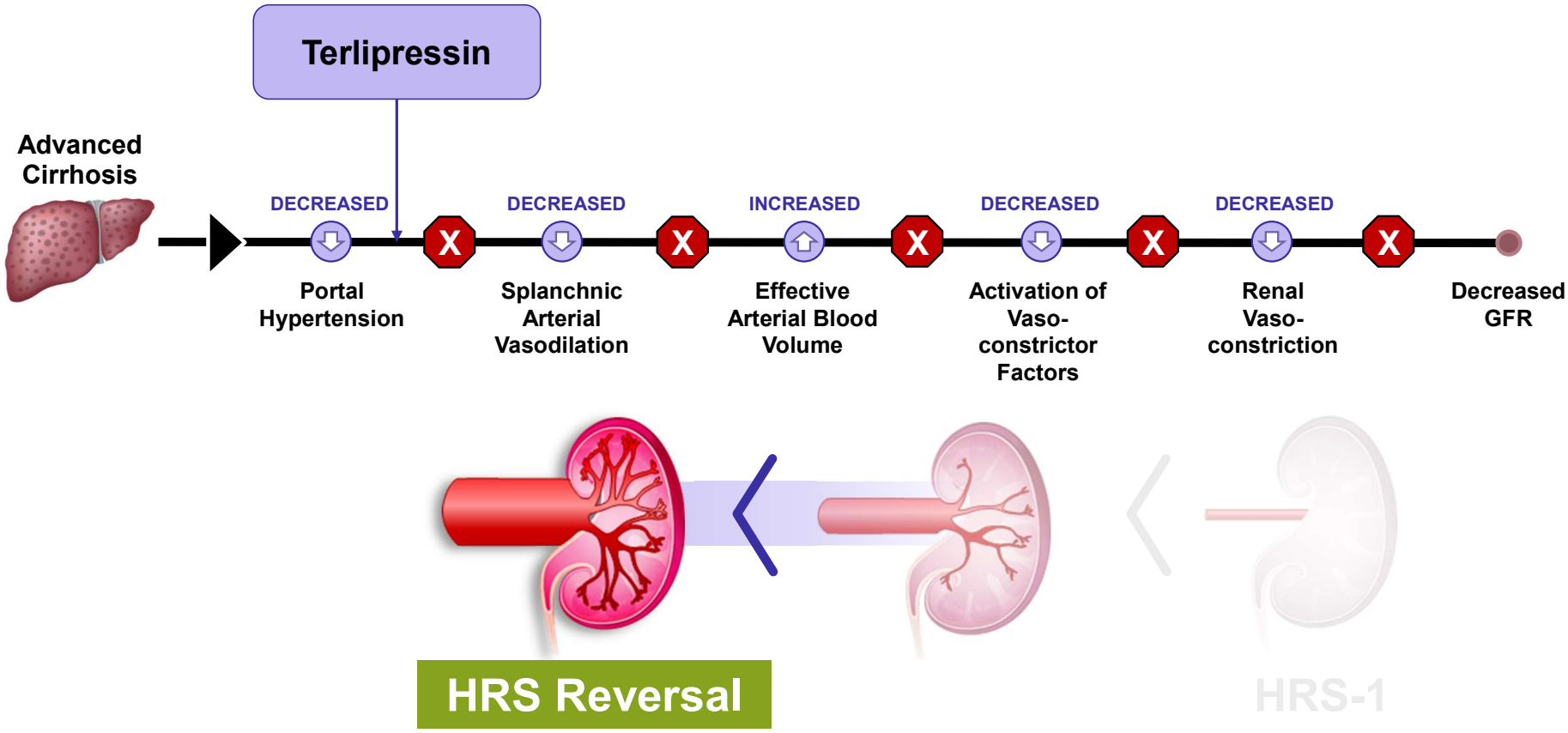
- **V1 receptor (vascular smooth muscle)**
  - Vasoconstriction
  - Increases mean arterial pressure
  - Reduces portal inflow and portal pressure
- **V2 receptor (renal tubules)**
  - Antidiuretic effect

MOA of Terlipressin: Splanchnic Vasoconstriction



Based on Wong F. *Nat Rev Gastroenterol Hepatol*. 2012;9:382-91.

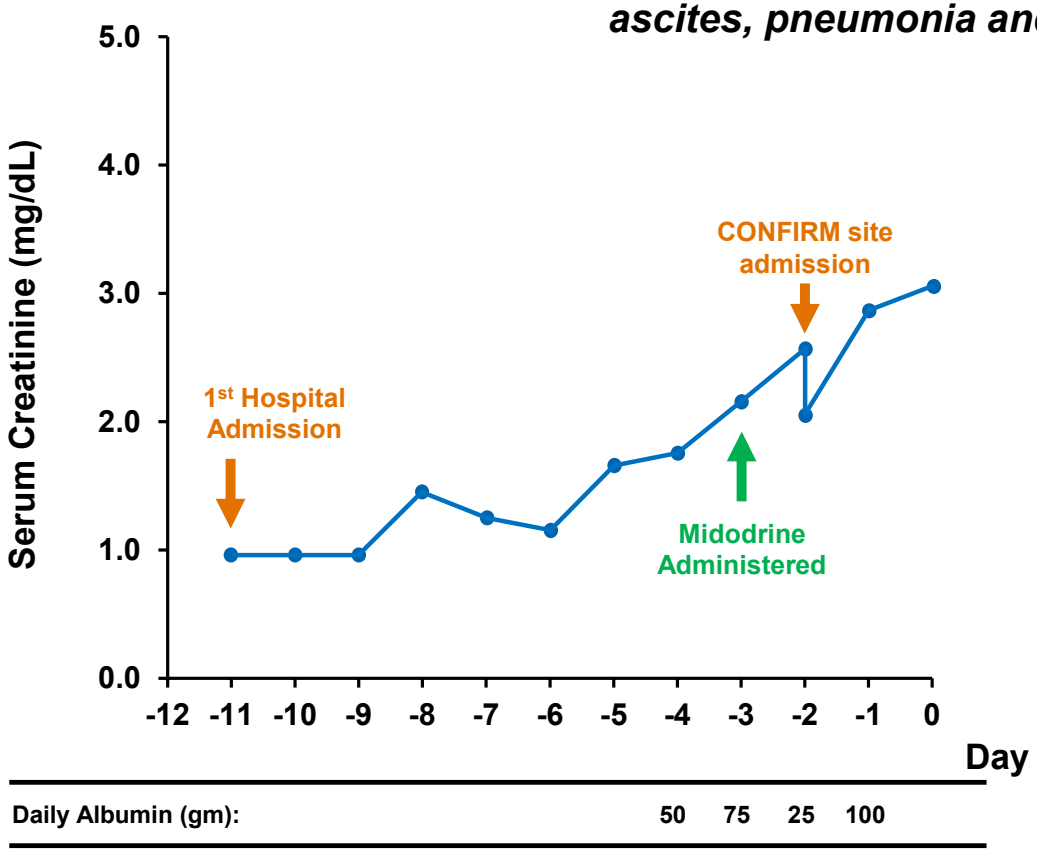
MOA of Terlipressin: Improve Renal Perfusion



Based on Wong F. *Nat Rev Gastroenterol Hepatol*. 2012;9:382-91.

CONFIRM Study Case: 48-Year-Old Male With Cirrhosis

48-year-old male with alcoholic cirrhosis, alcoholic hepatitis, ascites, pneumonia and acute kidney injury



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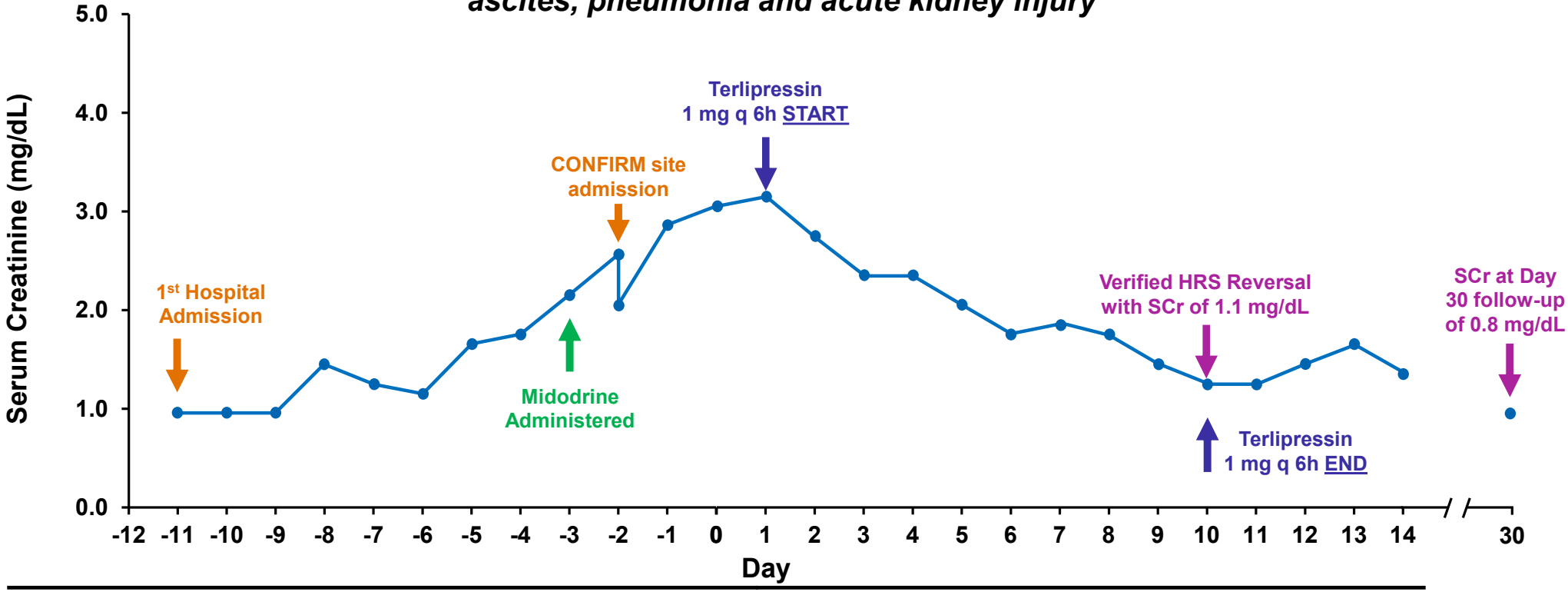

Daily Albumin (gm):	50	75	25	100	50	50	50	50	50	50	50	50	50	50

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Conclusions

- **HRS-1 is a rare life-threatening complication of decompensated cirrhosis**
- **No approved treatment for HRS-1 in US**
  - Physicians unable to treat a potentially reversible condition
- **Unmet need to improve kidney function and reverse HRS-1**
  - Facilitate medical management
  - Improve renal function and transplant outcomes

Efficacy


Khurram Jamil, MD

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Vice President, Clinical Research in Hepatology
Critical Care Division
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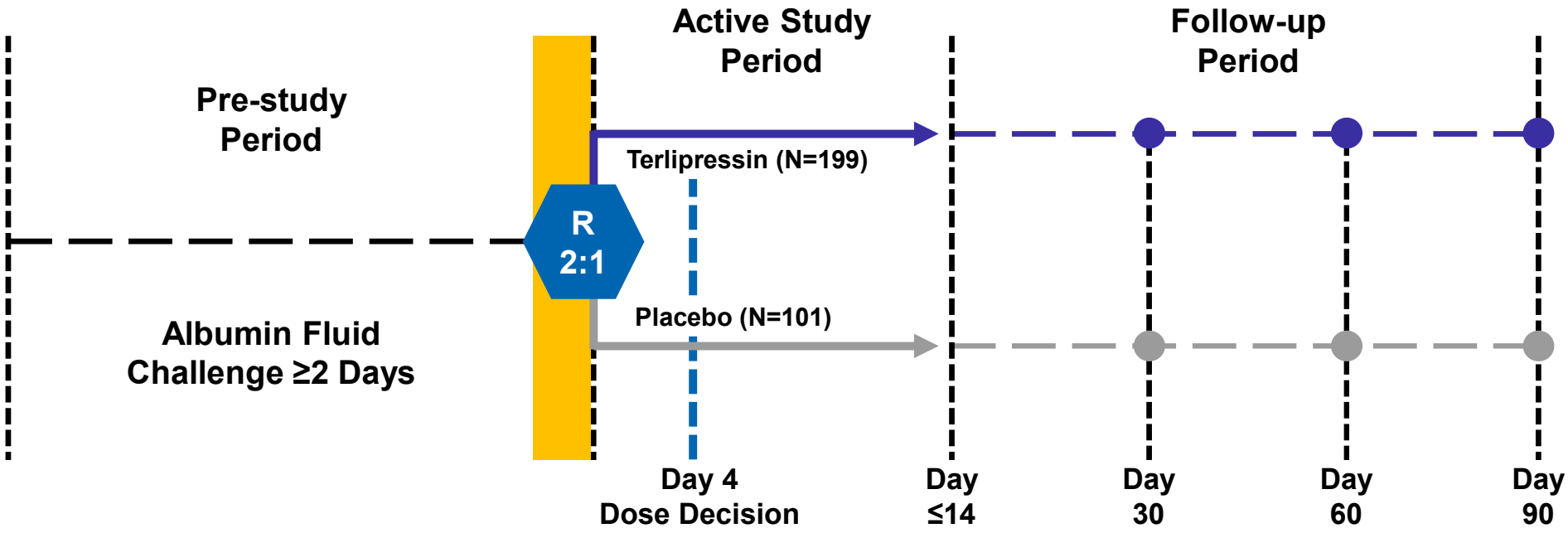
Terlipressin Phase 3 Program

Three Randomized Controlled Trials

- **Similar designs**
  - Small differences from evolving knowledge
- **Similar populations**
  - Subjects with cirrhosis, ascites and HRS-1
- **Similar treatment regimens**
  - 1-2 mg IV every 6 hours
  - Albumin was strongly recommended per treatment guidelines

CONFIRM Study Design



Primary Efficacy Endpoints
Phase 3 Studies of Terlipressin

OT-0401 Study
Sep 2004 – Aug 2006

Endpoint	Treatment Success at Day 14 Alive with HRS reversal
SCr Requirements	SCr ≤1.5 mg/dL ≥2 values
SCr Timing	48 ± 8 hours apart
Clinical Requirements	Without dialysis or HRS recurrence (SCr value at Day 14 <2.5 mg/dL)

Note: Up to Day 14 or discharge

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SCr Timing	**48 ± 8 hours apart**
Clinical Requirements	**Without dialysis or HRS recurrence (SCr value at Day 14 <2.5 mg/dL)**

- **Original analysis**
  - Double rate of success but not statistically significant
  - Logistical issues collecting data required for primary endpoint
    - E.g. required Day 14 SCr difficult to collect in subjects discharged prior to Day 14
- **FDA agreed to collection of additional post treatment SCr data**
  - From existing medical records for all subjects
  - Predefined threshold of SCr improvement
- **Reanalysis**
  - Two additional terlipressin subjects with treatment success
  - No additional on placebo
- **Agency accepted as confirmatory evidence of efficacy**
  - Complete response letter required one more study at $p<0.05$
  - Pivotal CONFIRM study meets this requirement

Note: Up to Day 14 or discharge

Primary Efficacy Endpoints
Phase 3 Studies of Terlipressin

Endpoint	OT-0401 Study Sep 2004 – Aug 2006 Treatment Success at Day 14 Alive with HRS reversal	REVERSE Study Oct 2010 – May 2013 Confirmed HRS reversal
SCr Requirements	SCr ≤1.5 mg/dL ≥2 values	SCr of ≤1.5 mg/dL 2 values
SCr Timing	48 ± 8 hours apart	At least 48 hours apart[1]
Clinical Requirements	Without dialysis or HRS recurrence (SCr value at Day 14 <2.5 mg/dL)	N/A

1. 22 hours apart if subject has transplant or discharge

Note: Up to Day 14 or discharge

Primary Efficacy Endpoints Phase 3 Studies of Terlipressin

Endpoint	OT-0401 Study Sep 2004 – Aug 2006 Treatment Success at Day 14 Alive with HRS reversal	REVERSE Study Oct 2010 – May 2013 Confirmed HRS reversal	CONFIRM Study Jul 2016 – Jul 2019 Verified HRS reversal
SCr Requirements	SCr ≤1.5 mg/dL ≥2 values	SCr of ≤1.5 mg/dL 2 values	SCr ≤1.5 mg/dL 2 consecutive values
SCr Timing	48 ± 8 hours apart	At least 48 hours apart[1]	At least 2 hours apart, on treatment[2]
Clinical Requirements	Without dialysis or HRS recurrence (SCr value at Day 14 <2.5 mg/dL)	N/A	Alive without RRT ≥10 days

1. 22 hours apart if subject has transplant or discharge
2. On treatment defined as up to 24 hours after the final dose of study drug; SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use were excluded from primary endpoint analysis

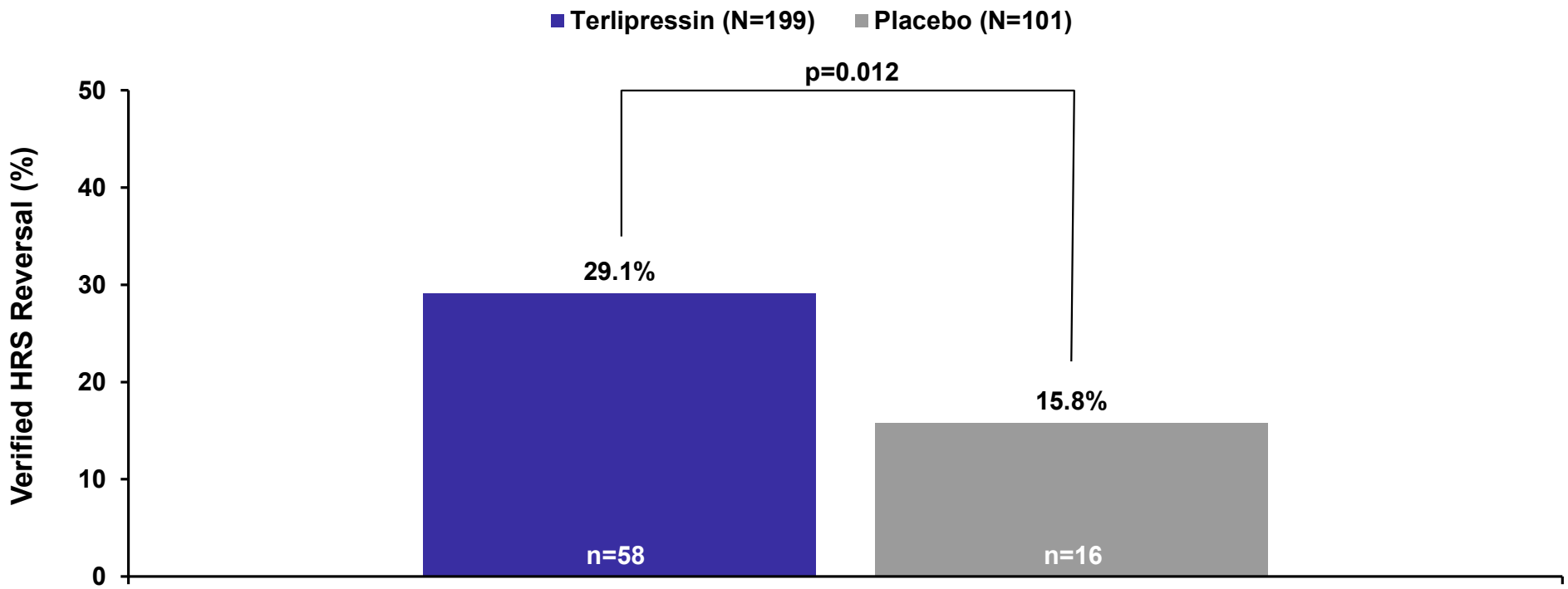
Note: Up to Day 14 or discharge

Demographics and Baseline Characteristics
CONFIRM Study

Parameter	Terlipressin N=199	Placebo N=101
Age, mean (SD), years	54.0 (11.3)	53.6 (11.8)
Sex, %		
Male	60.3	58.4
Alcoholic hepatitis present, %	40.7	38.6
Serum creatinine, mg/dL		
Mean (SD)	3.5 (1.0)	3.5 (1.1)
Minimum, maximum	2.3, 6.9	2.1, 6.2
SIRS, %	42.2	47.5
MELD score, mean (SD)	32.7 (6.6)[1]	33.1 (6.2)[2]
Baseline ACLF Grade 3, %	20.1	17.8
Bilirubin, mean (SD), mg/dL	13.0 (13.4)[3]	15.2 (15.8)[4]
CLIF-SOFA score, mean (SD)	10.4 (2.4)[5]	10.8 (2.5)[6]

1. n=177; 2. n=88; 3 n=188; 4 n=99; 5. n=107; 6. n=58
CLIF-SOFA, chronic liver failure-sequential organ failure assessment; MELD, model for end-stage liver disease; SIRS, systemic inflammatory response syndrome; ACLF, Acute on Chronic Liver Failure

Primary Endpoint: Verified HRS Reversal
CONFIRM Study



Z score=2.52618

Secondary Endpoints
CONFIRM Study

Endpoint	Definition
HRS Reversal	Subjects with a SCr value ≤1.5 mg/dL while receiving treatment by Day 14 or discharge
Durability of HRS Reversal	Percentage of subjects with HRS reversal without RRT to Day 30
Incidence of HRS Reversal in the Systemic Inflammatory Response Syndrome (SIRS) Subgroup	Percentage of SIRS subjects with HRS reversal
Incidence of Verified HRS Reversal Without Recurrence	No recurrence of HRS by Day 30

Secondary Endpoint Results
CONFIRM Study (ITT Population)

	Terlipressin n=199 %	Placebo N=101 %	P-value[1]
HRS Reversal (SCr ≤1.5)	36.2	16.8	<0.001
Durability of HRS Reversal (No RRT for 30 days)	31.7	15.8	0.003
HRS Reversal in the SIRS Subgroup	33.3	6.3	<0.001
Verified HRS Reversal With No Recurrence of HRS by Day 30	24.1	15.8	0.092

1. From a CMH Test stratified by qualifying SCr (<3.4 vs ≥3.4 mg/dL) and prior LVP within 14 days of randomization (at least one single event of ≥4 vs <4 L).

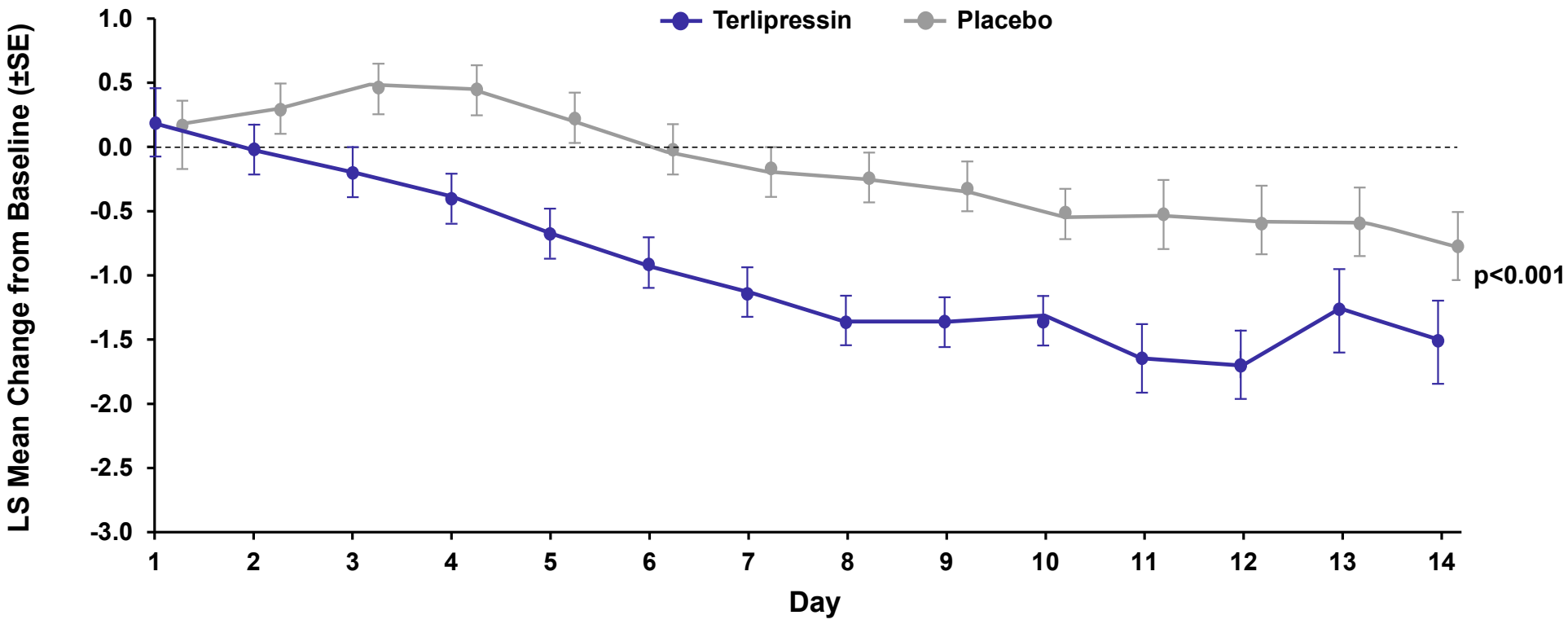
Pre-specified Renal Function Endpoints

- Change in renal function (SCr) from baseline through end of treatment as repeated measure analysis
- Incidence of greater than 30% improvement in SCr
- Change from baseline through the end of treatment in creatinine clearance (CrCl)
- Full response and partial response as per ICA Guidelines

ICA=International Club of Ascites

Change in Serum Creatinine, Baseline Through Day 14

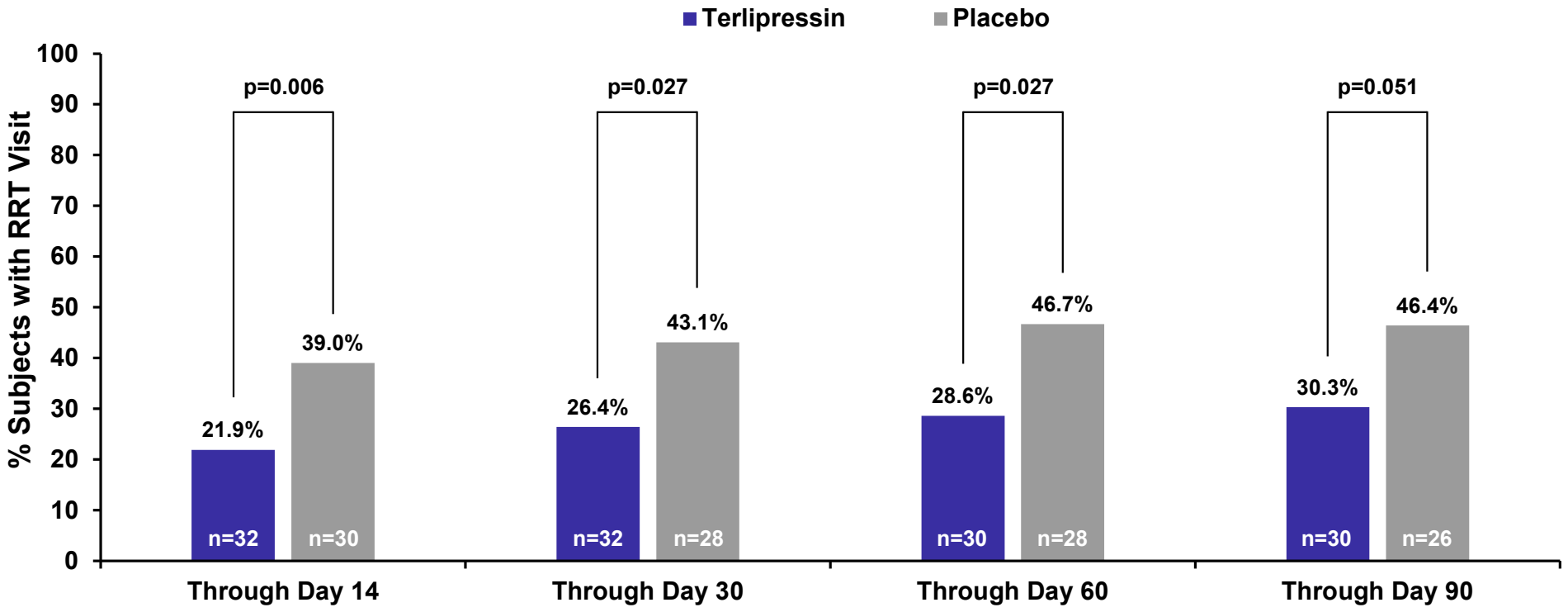
CONFIRM Study – Repeated Measures Analysis (ITT Population)



p-value is nominal

Incidence of RRT in Subjects Alive Through Day 90

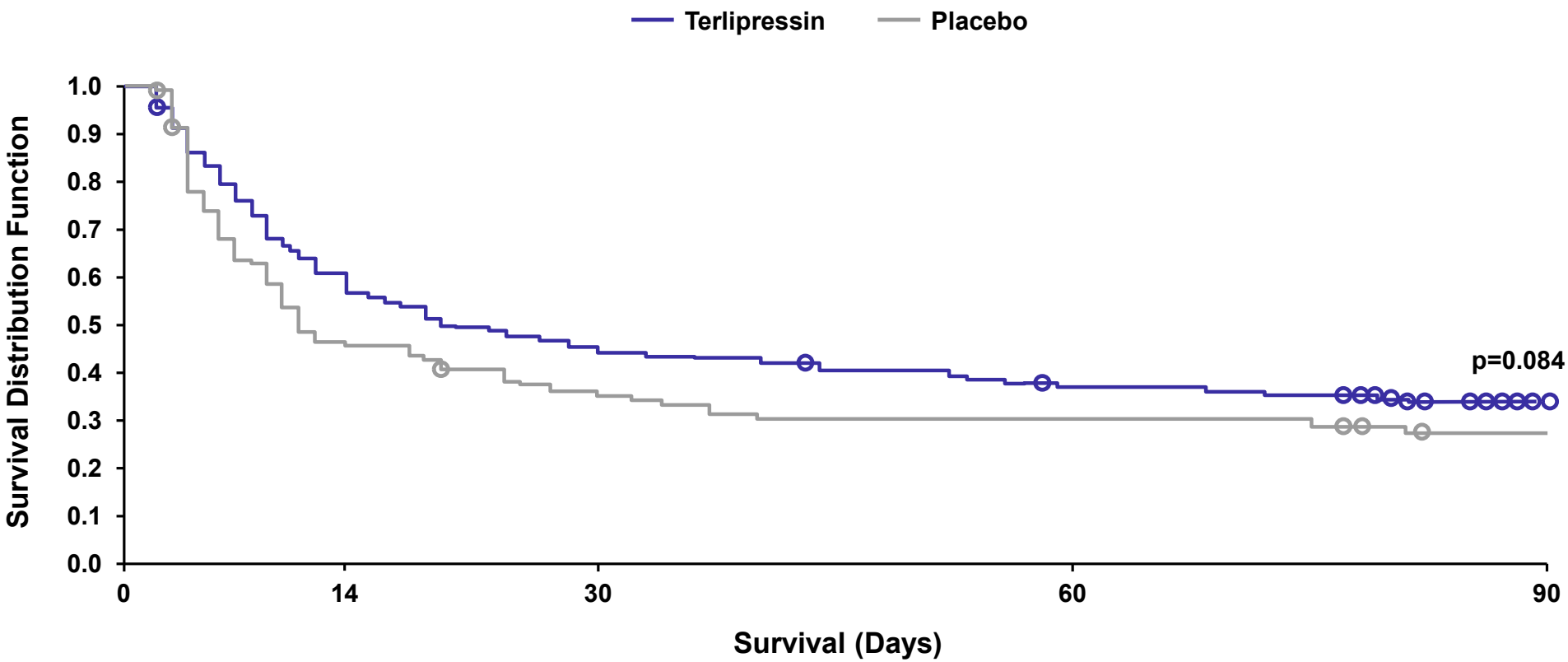
CONFIRM Study (ITT Population)



p-values are nominal

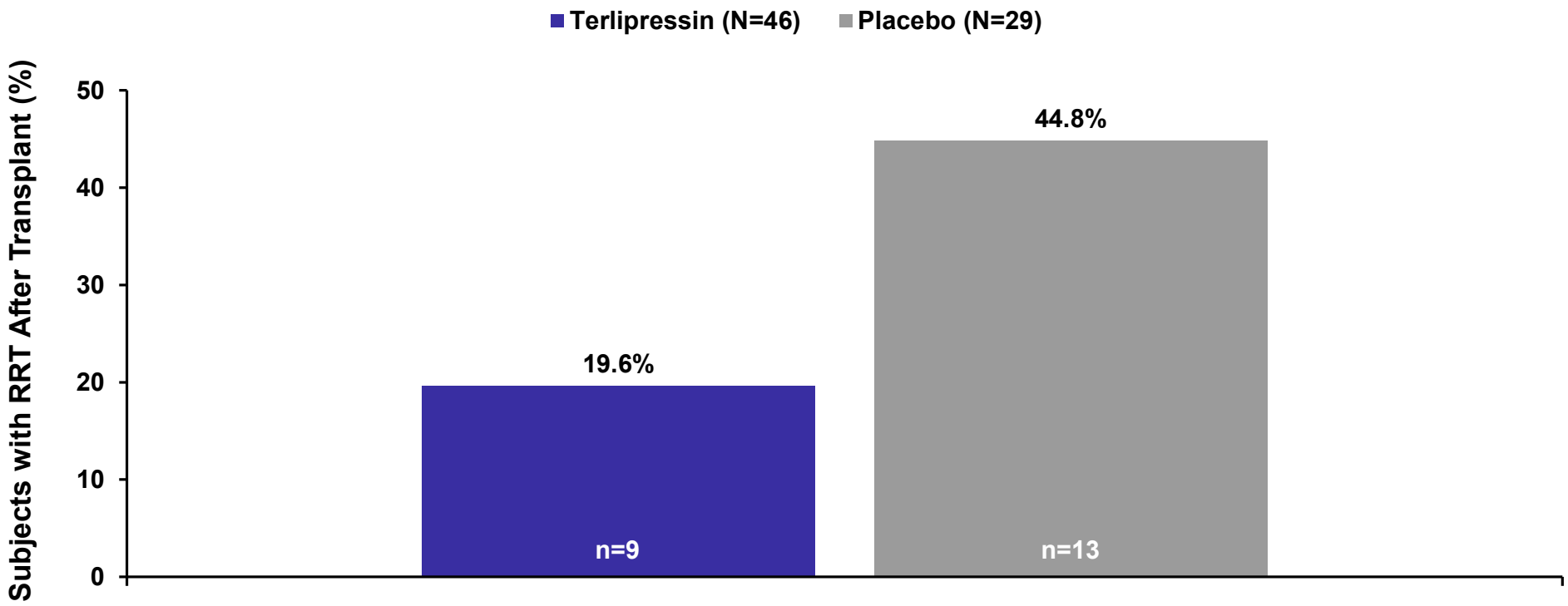
p-values from a Cochran-Mantel-Haenszel (CMH) Test stratified by qualifying serum creatinine (<3.4 vs ≥3.4 mg/dL) and prior large volume paracentesis (LVP) within 14 days of randomization (at least one single event of ≥4 vs <4 L).

RRT-free Survival up to Day 90
CONFIRM Study (ITT Population)

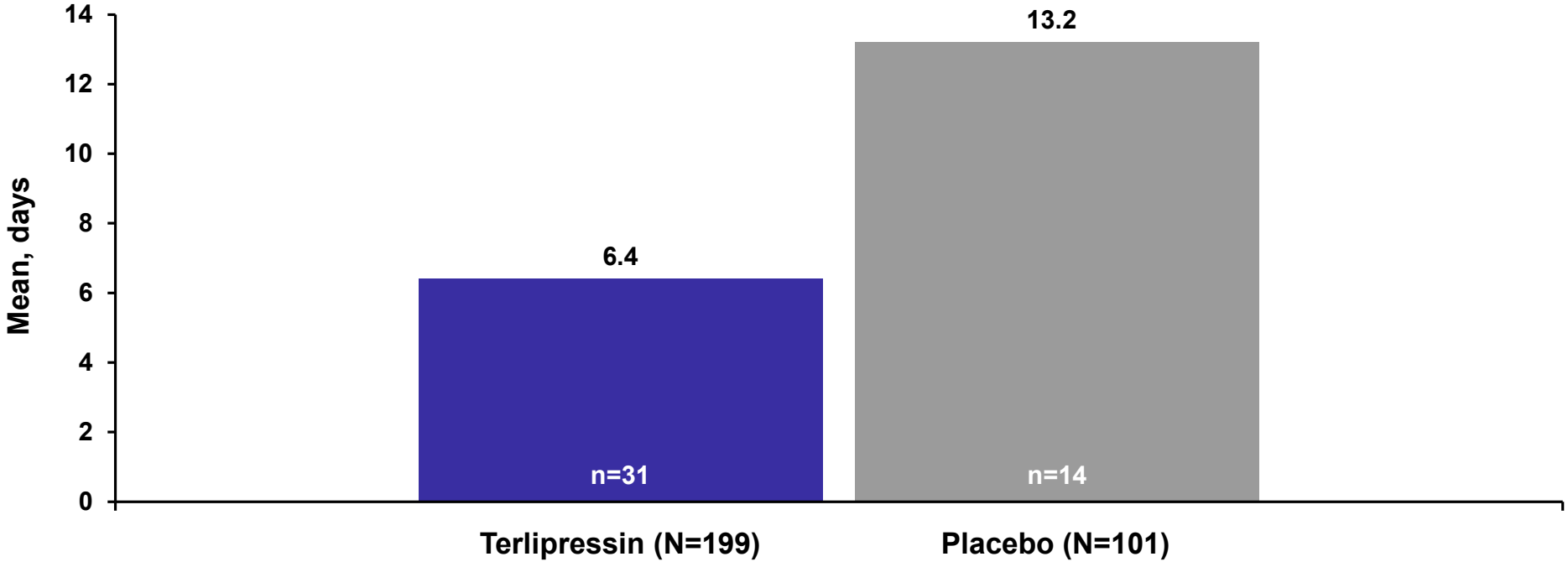


Nominal p-value based on two-sample log rank test stratified by qualifying SCr (< 3.4 vs ≥ 3.4 mg/dL) and prior large volume paracentesis (LVP) within 14 days of randomization (at least one single event of ≥ 4 vs < 4 L).

Incidence of RRT Post Liver Transplant
CONFIRM Study (ITT Population)



Intensive Care Unit Length of Stay
CONFIRM Study (ITT Population)



ICU admission, %	15.6	13.9
Time from ICU admission to death (days), mean	12.2	13.0

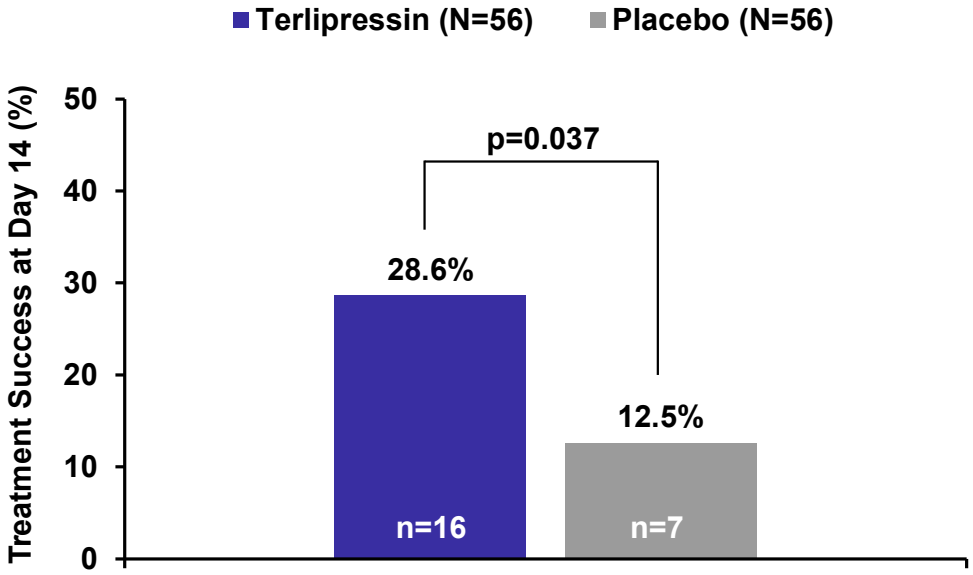
Outcomes for Subjects Admitted to ICU
CONFIRM Study (ITT Population)

	Subjects with ICU Admission	
	Terlipressin N=31 %	Placebo N=14 %
Alive without RRT or Transplant at Day 14	29.0	7.1
Alive without RRT or Transplant at Day 30	12.9	0.0

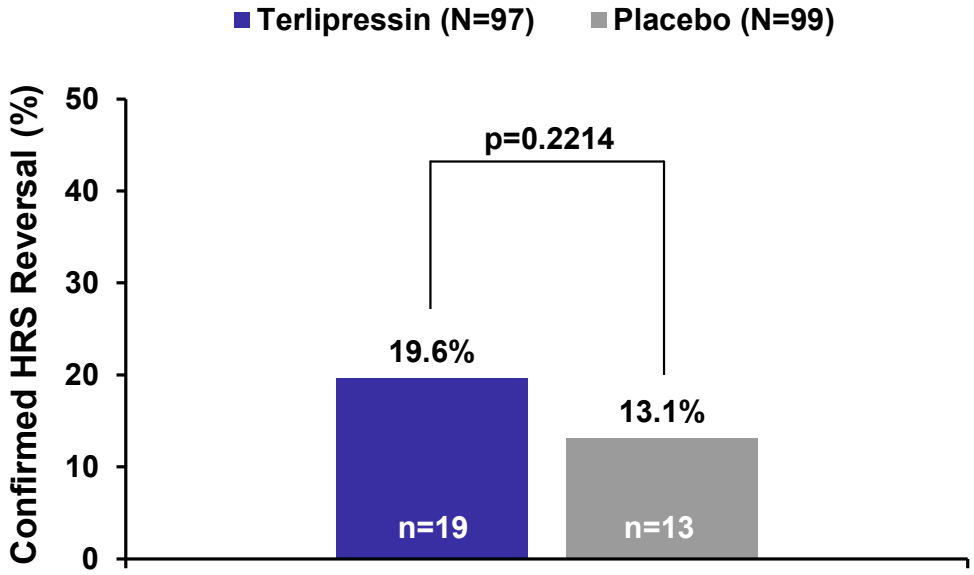
Weil et al. Ann. *Intensive Care* (2017) 7:33

Primary Endpoint Results
OT-0401 and REVERSE Studies

OT-0401 Study
Treatment Success at Day 14



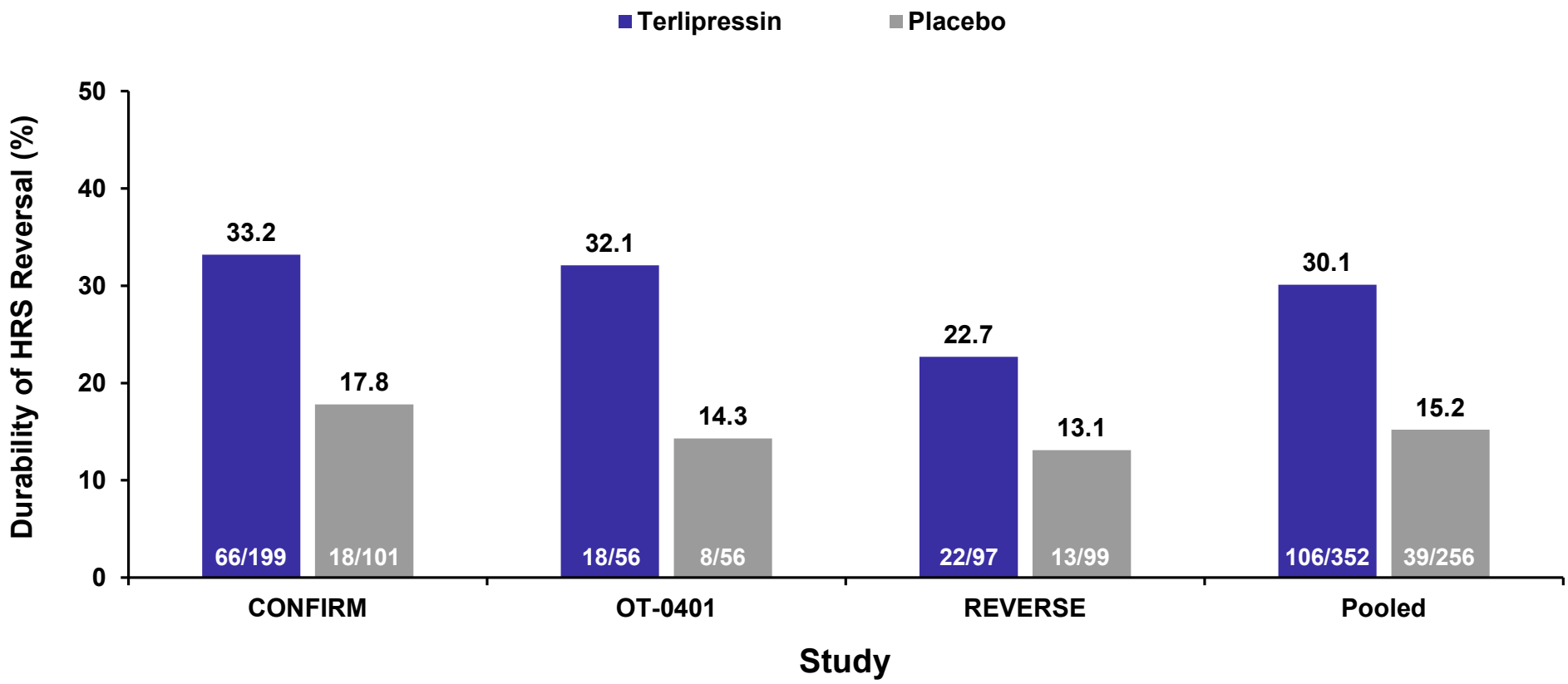
REVERSE Study
Confirmed HRS Reversal



Outcomes In Pooled Analyses

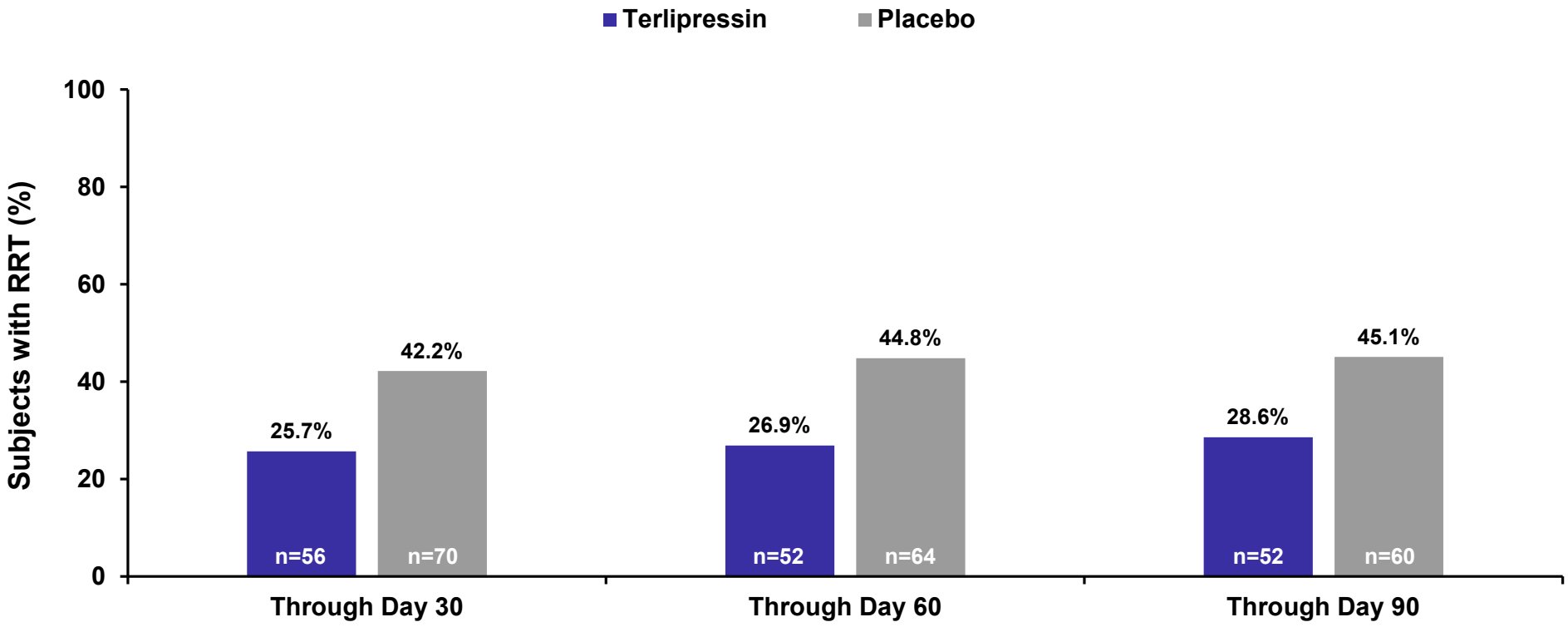
Durability of HRS Reversal

CONFIRM, OT-0401, REVERSE Studies, and Pooled Population (ITT Population)



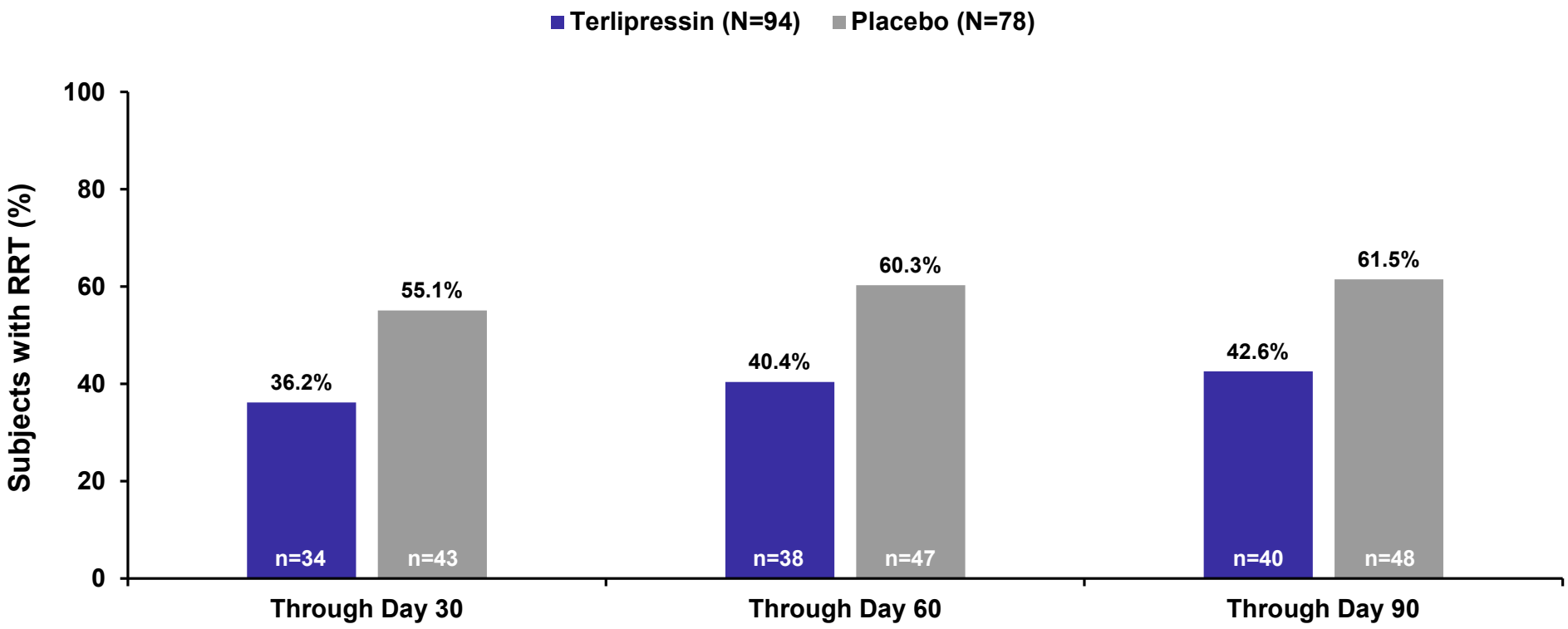
Incidence of RRT in Subjects Alive Through Day 90

Pooled ITT Population



Note: REVERSE only captures yes/no if there was an RRT by these follow up days. This information is used instead of the study day.

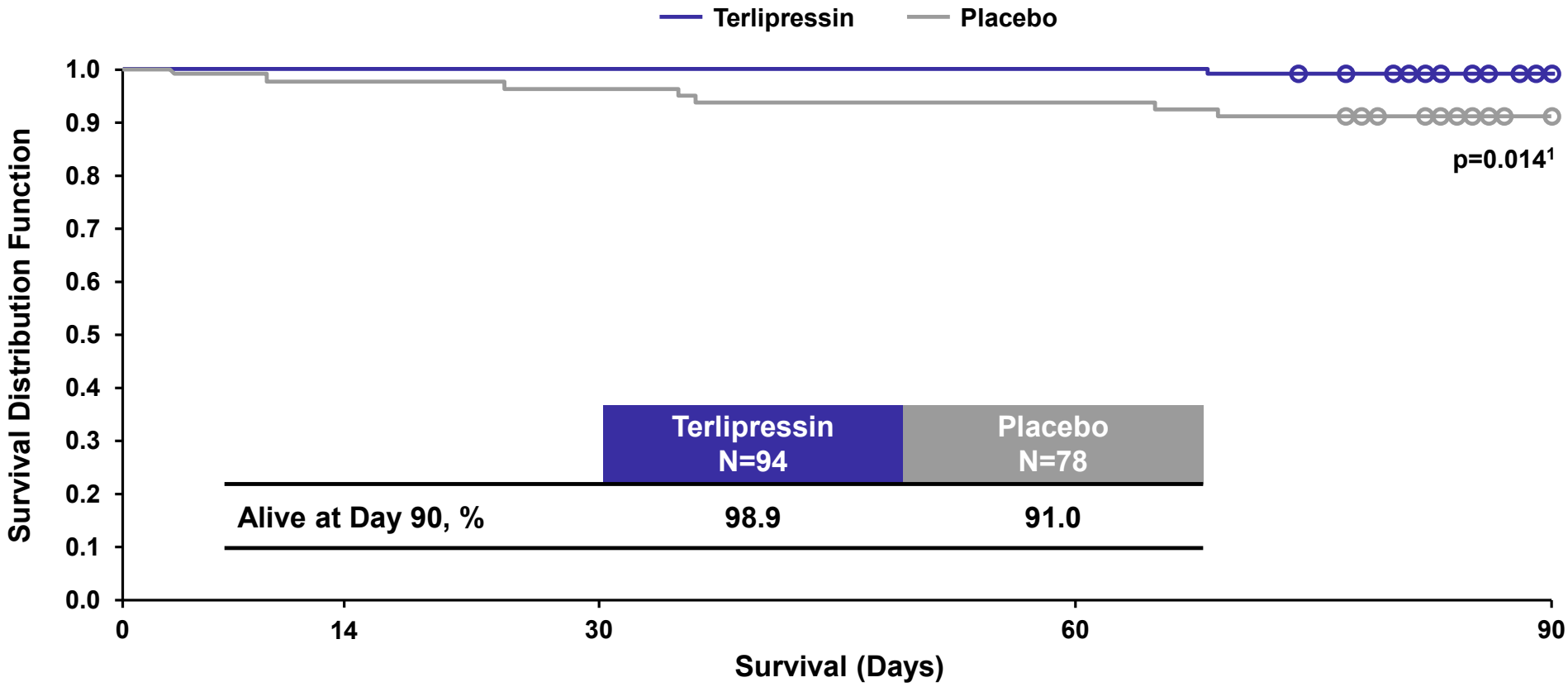
Incidence of RRT Through Day 90 for Transplanted Subjects
Pooled ITT Population



Note: For OT-0401 and CONFIRM, dates/times were used to determine 30, 60, and 90 days. For REVERSE, RRT was recorded at the visits for days 30, 60, and 90 without an RRT date

Survival of Transplanted Subjects Through Day 90

Pooled ITT Population



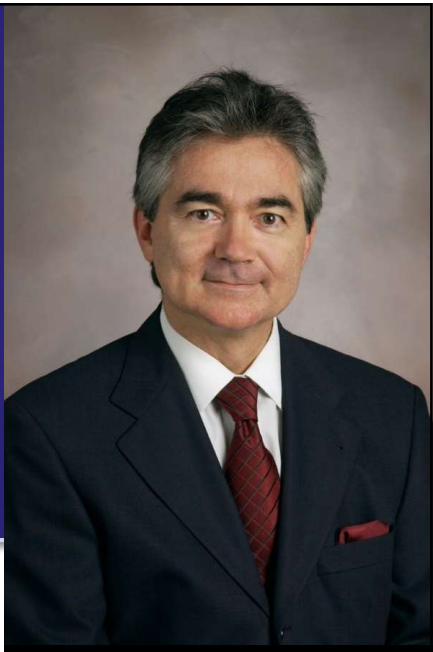
1. The p-value comparing the survival estimates is from a two-sample log-rank test.

Lee et al., US trends for transplant outcomes. *JAMA internal medicine* 2019

Terlipressin Efficacy Conclusions

- **Positive pivotal and supportive Phase 3 study results**
  - Higher rate of HRS Reversal and greater reduction in SCr
- **Improved clinical outcomes**
  - Decreased incidence of RRT
  - Improved RRT-free survival
  - Shorter ICU stays
- **Clinical benefit in transplant subjects**
  - Decreased incidence of RRT post transplant
  - Improved survival in transplant recipients

Safety



Chris Pappas, MD

Chris Pappas, MD

Clinical Hepatologist
Consultant, Mallinckrodt

Subject Distribution Across Studies

	Terlipressin N	Placebo N
Overall number of subjects (pooled)	349	249
CONFIRM study	200	99
OT-0401 study	56	55
REVERSE study	93	95

Summary of Exposure to Treatment
Integrated Studies (Safety Population)

Parameter	Terlipressin N=349	Placebo N=249
Daily exposure (mg/day)		
Mean (SD)	3.6 (1.39)	3.8 (1.46)
Duration[1,2] (days)		
Mean (SD)	6.2 (4.39)	6.0 (3.86)
Min, max	1.0, 25.0	1.0, 19.0

1. For retreated subjects, data are combined from initial and retreatment periods.
2. Includes number of days the subject received ≥1 dose of study drug.

Overview of Adverse Event Profile
Integrated Studies (Safety Population)

Safety Parameter[1]	Terlipressin N=349 %	Placebo N=249 %
AEs up to 7 days post-treatment	91.1	90.4
SAEs up to 30 days post-treatment	65.0	59.8
Permanent withdrawals due to adverse events	13.5	5.2
Gastrointestinal disorders	4.6	1.2
Ischemia-related AEs	3.7	0.4
Respiratory disorders	3.4	0.8
Other	1.8	2.8

1. Subjects with multiple AEs of one preferred term are counted once.

Deaths Due to Adverse Events
Integrated and Individual Studies (Safety Population)

	CONFIRM Study		OT-0401 Study		REVERSE Study		Integrated Study	
	Terlipressin N=200 %	Placebo N=99 %	Terlipressin N=56 %	Placebo N=55 %	Terlipressin N=93 %	Placebo N=95 %	Terlipressin N=349 %	Placebo N=249 %
Deaths up to 30 days post-treatment	41.5	40.4	48.2	49.1	37.6	35.8	41.5	40.6
AEs leading to death up to 90 days from the start of study treatment	51.0	44.4	48.2	50.9	43.0	45.3	48.4	46.2

Adverse Events (≥5%) Leading to Death up to 30 Days Post-treatment
Integrated Studies (Safety Population)

	Terlipressin N=349 %	Placebo N=249 %
Total with AE leading to death	41.5	40.6
Chronic hepatic failure + hepatic failure	11.7	14.9
Respiratory failure + acute respiratory failure	7.7	2.0
Multiple organ dysfunction syndrome	6.3	3.2
Sepsis + septic shock + urosepsis	5.7	1.6

Most Common Adverse Events (≥10%)
Integrated Studies (Safety Population)

Preferred Term[1,2]	Terlipressin N=349 %	Placebo N=249 %
Abdominal pain	21.5	12.4
Nausea	15.2	12.0
Diarrhea	14.9	5.6
Dyspnea	12.0	6.0
Hypotension	11.7	7.6
Vomiting	10.3	6.4
Hepatic encephalopathy	8.6	11.2

1. Up to 7 days after the end of treatment
2. Subjects with multiple AEs of one preferred term are counted once

Adverse Events Occurring at ≥5% Higher Incidence
Integrated Studies (Safety Population)

Preferred Term[1,2]	Terlipressin N=349 %	Placebo N=249 %
Abdominal pain	21.5	12.4
Diarrhea	14.9	5.6
Dyspnea	12.0	6.0
Bradycardia	6.3	0.8

1. Up to 7 days after the end of treatment
2. Subjects with multiple AEs of one preferred term are counted once

Most Common Serious Adverse Events (≥5%)
Integrated Studies (Safety Population)

Preferred Term[1,2]	Terlipressin N=349 %	Placebo N=249 %
Total with any SAEs	**65.0**	**59.8**
Respiratory failure	**8.3**	**2.4**
Multiple organ dysfunction syndrome	**7.4**	**3.2**
Chronic hepatic failure	**6.0**	**6.0**
Hepatic failure	**6.0**	**9.2**
Sepsis	**5.2**	**1.6**

1. Up to 30 days posttreatment.
2. Subjects with multiple AEs of one preferred term are counted once.

Most Common Serious Adverse Events (≥5%)
Integrated Studies (Safety Population)

Preferred Term[1,2]	Terlipressin N=349 %	Placebo N=249 %
Total with any SAEs	65.0	59.8
Respiratory failure	8.3	2.4
Multiple organ dysfunction syndrome	7.4	3.2
Chronic hepatic failure	6.0	6.0
Hepatic failure	6.0	9.2
Sepsis	5.2	1.6

1. Up to 30 days posttreatment.
2. Subjects with multiple AEs of one preferred term are counted once.

Cardiopulmonary Complications of Decompensated Cirrhosis

- Fluid overload
- Cirrhotic cardiomyopathy
- Intrapulmonary shunting
- Porto-pulmonary hypertension
- Ascites leading to pleural effusions
- Increased aspiration risk

Respiratory Failure SAEs and Deaths
Integrated Studies (Safety Population)

	Terlipressin N=349 %	Placebo N=249 %
Serious adverse events		
Respiratory failure	**11.2**	**4.4**
Respiratory failure	**8.3**	**2.4**
Acute respiratory failure	**3.2**	**2.0**
AEs leading to death		
Respiratory failure	**7.7**	**2.0**
Respiratory failure	**5.4**	**1.2**
Acute respiratory failure	**2.3**	**0.8**

Respiratory Failure and Acute Respiratory Failure AEs and Deaths
CONFIRM, OT-0401, REVERSE, and Integrated Studies (Safety Population)

	OT-0401 (2004 – 2006)		REVERSE (2010 – 2013)		CONFIRM (2016 – 2019)	
Preferred Term[1,2]	Terlipressin N=56 %	Placebo N=55 %	Terlipressin N=93 %	Placebo N=95 %	Terlipressin N=200 %	Placebo N=99 %
SAE						
Respiratory failure	5.4	3.6	6.5	1.1	10.0	3.0
Acute respiratory failure	0	0	3.2	3.2	4.0	2.0
AE leading to death						
Respiratory failure	3.6	3.6	5.4	1.1	6.0	0
Acute respiratory failure	0	0	2.2	1.1	3.0	1.0

1. Up to 30 days posttreatment
2. Subjects with multiple AEs of one preferred term are counted onc.

Albumin Use in Clinical Practice

- **Increased use in clinical practice during development program**
  - CONFIRM > REVERSE > OT-0401
- **Changes in guidelines before REVERSE**
  - ICA 2007
- **Increased use prior to CONFIRM**
  - Literature supported higher use
    - Bernardi et al, 2012; Garcia-Martinez et al, 2013; Chasou et al, 2016

Prior Albumin Exposure
CONFIRM, OT-0401, and REVERSE Studies

	OT-0401 Study		REVERSE Study		CONFIRM Study	
	Terlipressin N=56	Placebo N=56	Terlipressin N=97	Placebo N=99	Terlipressin N=199	Placebo N=101
Overall subjects exposed to prior albumin (%)	64.3%	80.0%	100.0%	100.0%	99.0%	99.0%
Mean total prior albumin exposure (g)	-	-	243.2	218.1	335.0	370.7

Fluid Management Pre/Post DSMB Meeting

CONFIRM Study

	Before DSMB Meeting		After DSMB Meeting	
	Terlipressin N=87 %	Placebo N=44 %	Terlipressin N=112 %	Placebo N=57 %
Concomitant diuretics	23.0	15.9	27.7	10.5
Subjects receiving concomitant albumin	83.9	95.5	82.1	87.7
Subjects receiving >662.5 g of cumulative albumin	26.4	31.8	18.8	24.6

Respiratory Failure Deaths Pre/Post DSMB Meeting

CONFIRM Study

	Before DSMB Meeting		After DSMB Meeting	
	Terlipressin N=87 %	Placebo N=43 %	Terlipressin N=113 %	Placebo N=56 %
Acute respiratory failure or respiratory failure AE	11.5	0	7.1	1.8
Acute respiratory failure AE	4.6	0	1.8	1.8
Respiratory failure AE	6.9	0	5.3	0

Note: Subjects experiencing multiple episodes of a given adverse event are counted once within each preferred term and within each system organ class.

Incidence of Respiratory Failure SAEs by Total Prior Albumin Exposure

Safety Population

Total Prior Albumin Exposure	Terlipressin		Placebo		RD (95% CI)
	N	%	N	%	
Overall respiratory failures SAEs	349	12.6	249	7.6	5.0 (0.2, 9.8)
Albumin <175 g	55	10.9	58	10.3	0.6 (-11.0, 11.9)
Albumin 175 g to <300 g	90	12.2	51	7.8	4.4 (-5.6, 14.4)
Albumin 300 g to <423 g	85	12.9	53	5.7	7.3 (-2.2, 16.7)
Albumin ≥423 g	79	16.5	52	7.7	8.8 (-2.2, 19.7)

Respiratory Effects with Terlipressin Treatment

- **Increases cardiac afterload, effective circulating volume, preload**
- **Perturbs the perfusion/ventilation relationships in lung**
- **Increased risk of respiratory events in subjects with**
  - Advanced liver disease, particularly ACLF grade 3
  - Cardiorespiratory events
  - Upper GI hemorrhage
  - Increased hepatic encephalopathy

Selected SAEs by ACLF Grade (≥5% Incidence in Terlipressin ACLF3 Group)

CONFIRM Study (Safety Population)

	Baseline ACLF Grade 0-2		Baseline ACLF Grade 3	
	Terlipressin N=160 %	Placebo N=81 %	Terlipressin N=40 %	Placebo N=18 %
Overall	61.3	59.3	80.0	66.7
Respiratory failure	6.3	3.7	25.0	0
Multiple organ dysfunction syndrome	3.1	2.5	10.0	5.6
Abdominal pain	4.4	1.2	7.5	0
Hepatic failure	3.8	6.2	7.5	27.8
Sepsis	3.8	0	7.5	0
Gastrointestinal hemorrhage	3.1	0	7.5	0
Hepatic cirrhosis	1.9	2.5	7.5	0
Chronic hepatic failure	4.4	8.6	5.0	5.6
Acute respiratory failure	3.8	2.5	5.0	0
Shock	1.9	2.5	5.0	5.6
Cirrhosis alcoholic	1.3	1.2	5.0	11.1

Selected AEs Leading to Death by ACLF Grade (≥5% Incidence in Terlipressin ACLF3 Group)

CONFIRM Study (Safety Population)

	Baseline ACLF Grade 0-2		Baseline ACLF Grade 3	
	Terlipressin N=160 %	Placebo N=81 %	Terlipressin N=40 %	Placebo N=18 %
Overall	45.6	43.2	72.5	50.0
Respiratory failure	3.1	0	17.5	0
Multiple organ dysfunction syndrome	4.4	4.9	10.0	5.6
Chronic hepatic failure	6.9	8.6	7.5	5.6
Hepatic failure	5.0	6.2	7.5	22.2
Hepatic cirrhosis	3.1	2.5	7.5	0
Sepsis	1.3	0	7.5	0
Acute respiratory failure	2.5	1.2	5.0	0
Cirrhosis alcoholic	1.9	1.2	5.0	11.1

Infections and Infestations SOC Adverse Events

Integrated Studies (Safety Population)

	Terlipressin N=349 %	Placebo N=249 %
Infections and infestations	**26.1**	**21.3**

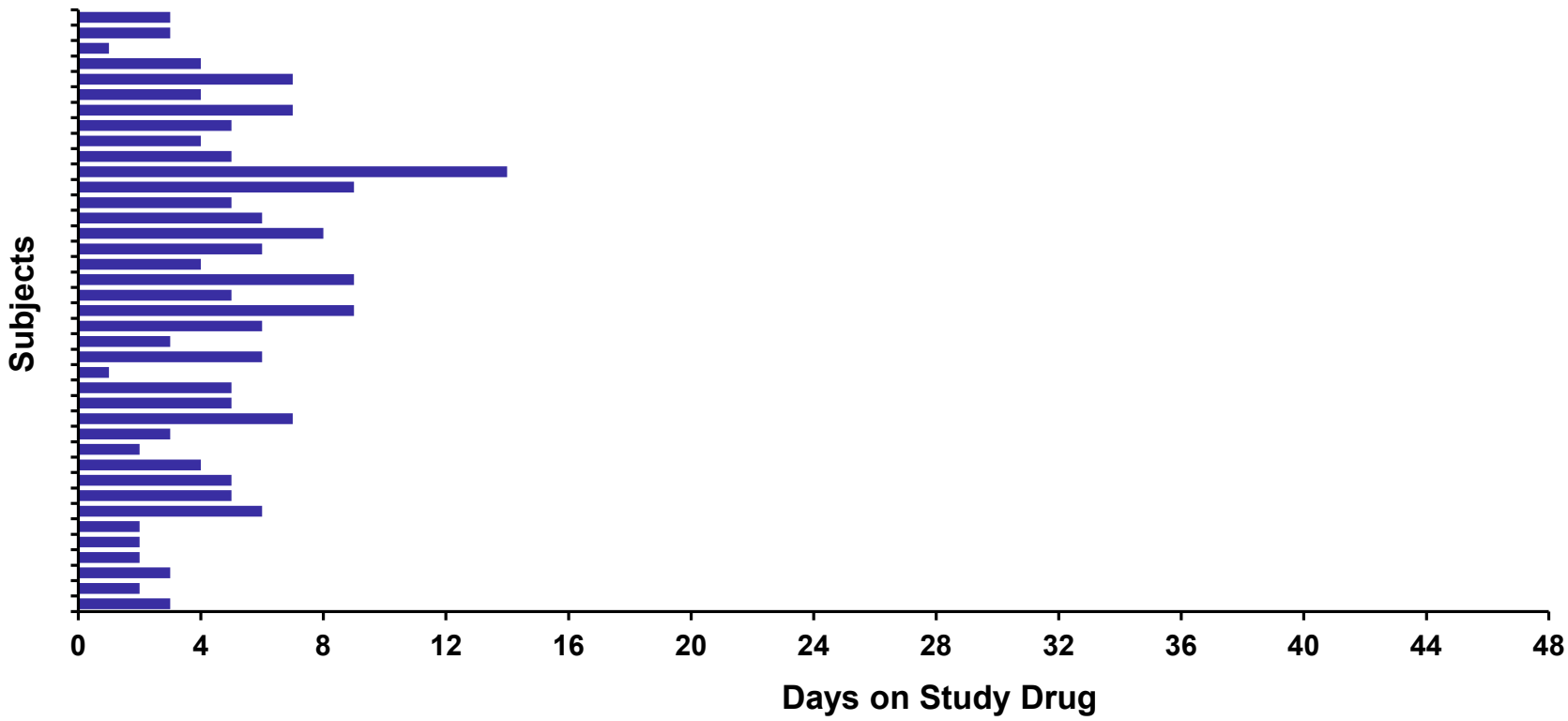
Sepsis Adverse Events and Deaths
Integrated Studies (Safety Population)

	Terlipressin N=349 %	Placebo N=249 %
AEs[1]		
Combined sepsis	9.7	4.0
Sepsis	6.3	3.2
Septic shock	2.9	1.2
Urosepsis	0.6	0.0
AEs leading to death[1]		
Combined sepsis	5.7	1.6
Sepsis	3.4	1.2
Septic shock	2.3	0.4
Urosepsis	0.0	0.0

1. Subjects reporting >1 AE are counted only once by the first AE reported.

Terlipressin Subjects with Sepsis AE

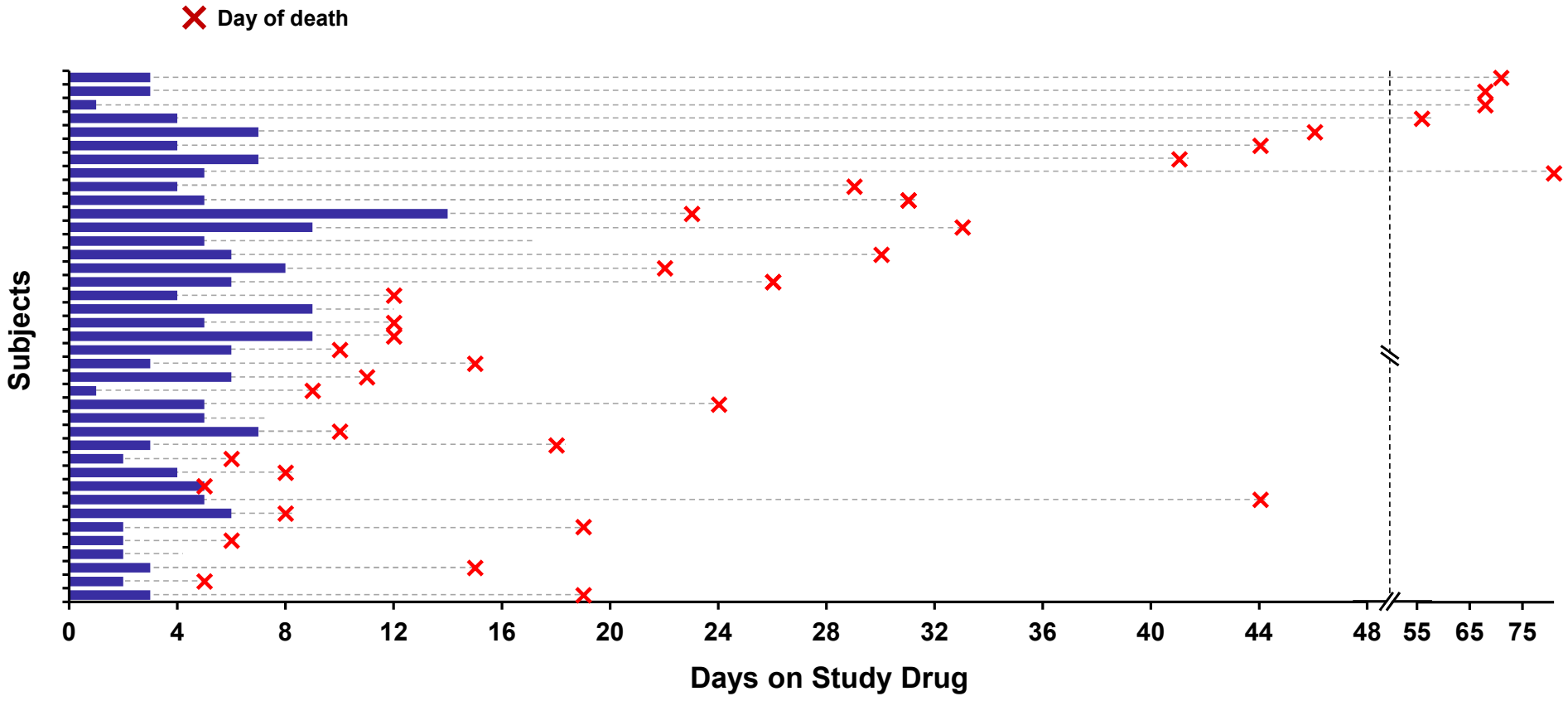
Integrated Studies (Safety Population)



Sepsis AE includes abdominal sepsis, enterococcal sepsis, klebsiella sepsis, septic shock, sepsis syndrome, sepsis, and urosepsis

Terlipressin Subjects with Sepsis AE

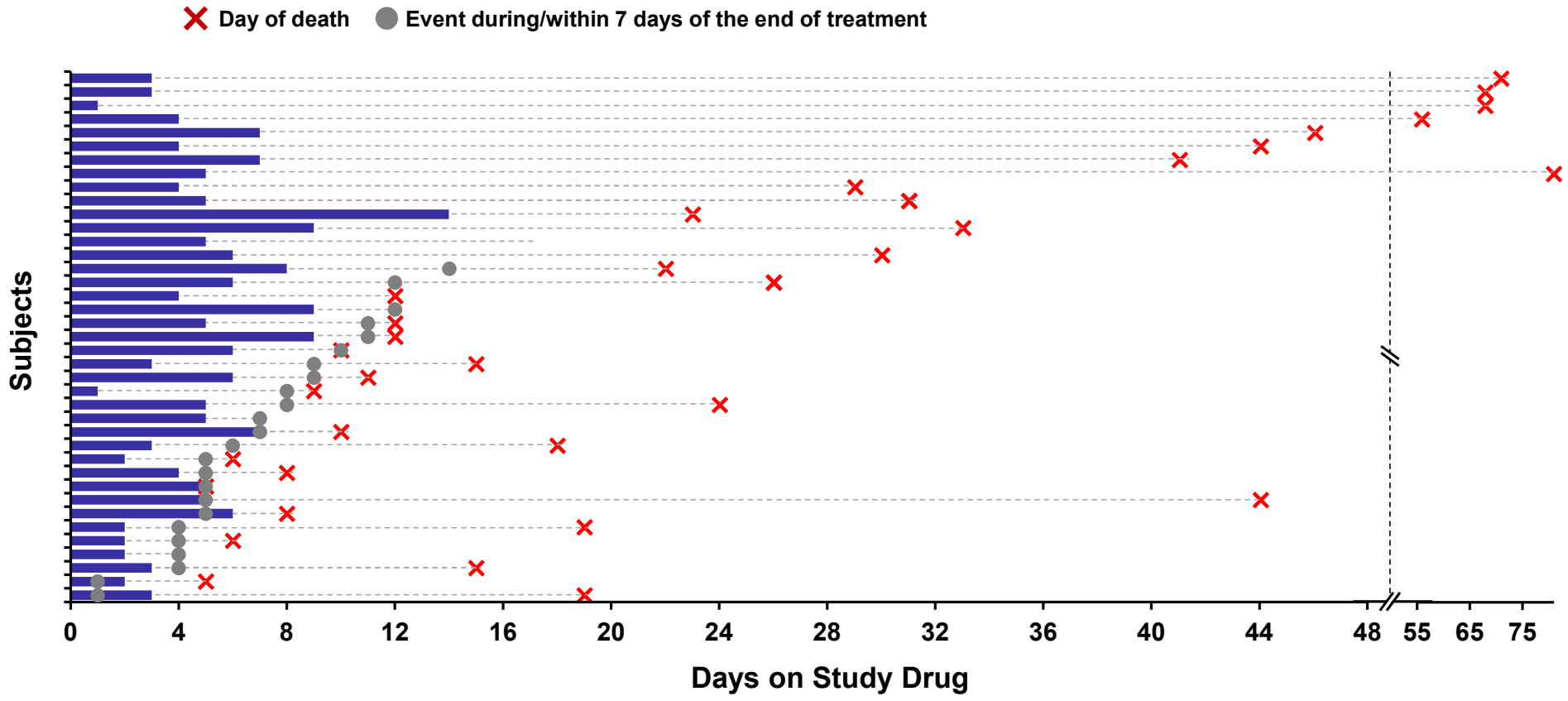
Integrated Studies (Safety Population)



Sepsis AE includes abdominal sepsis, enterococcal sepsis, klebsiella sepsis, septic shock, sepsis syndrome, sepsis, and urosepsis

Terlipressin Subjects with Sepsis AE

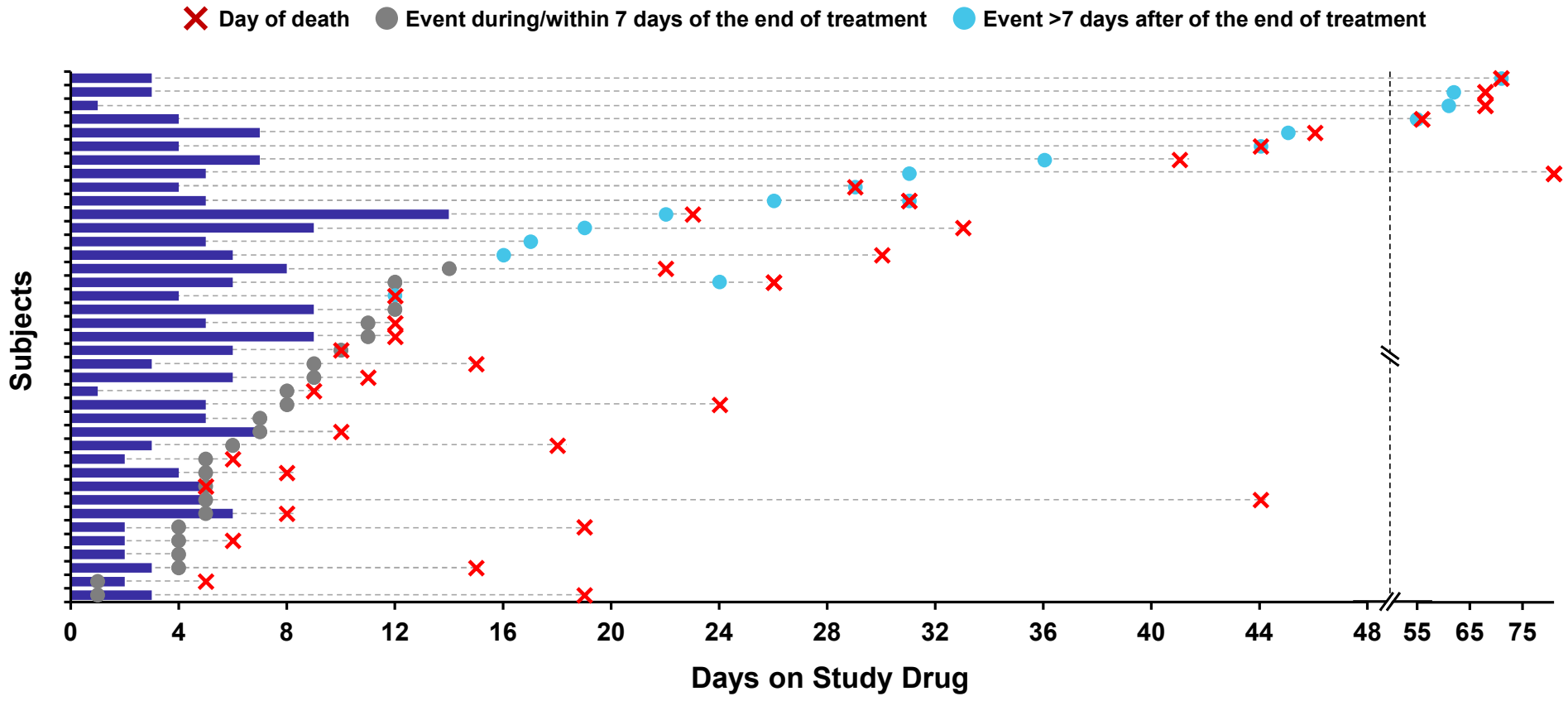
Integrated Studies (Safety Population)



Sepsis AE includes abdominal sepsis, enterococcal sepsis, klebsiella sepsis, septic shock, sepsis syndrome, sepsis, and urosepsis

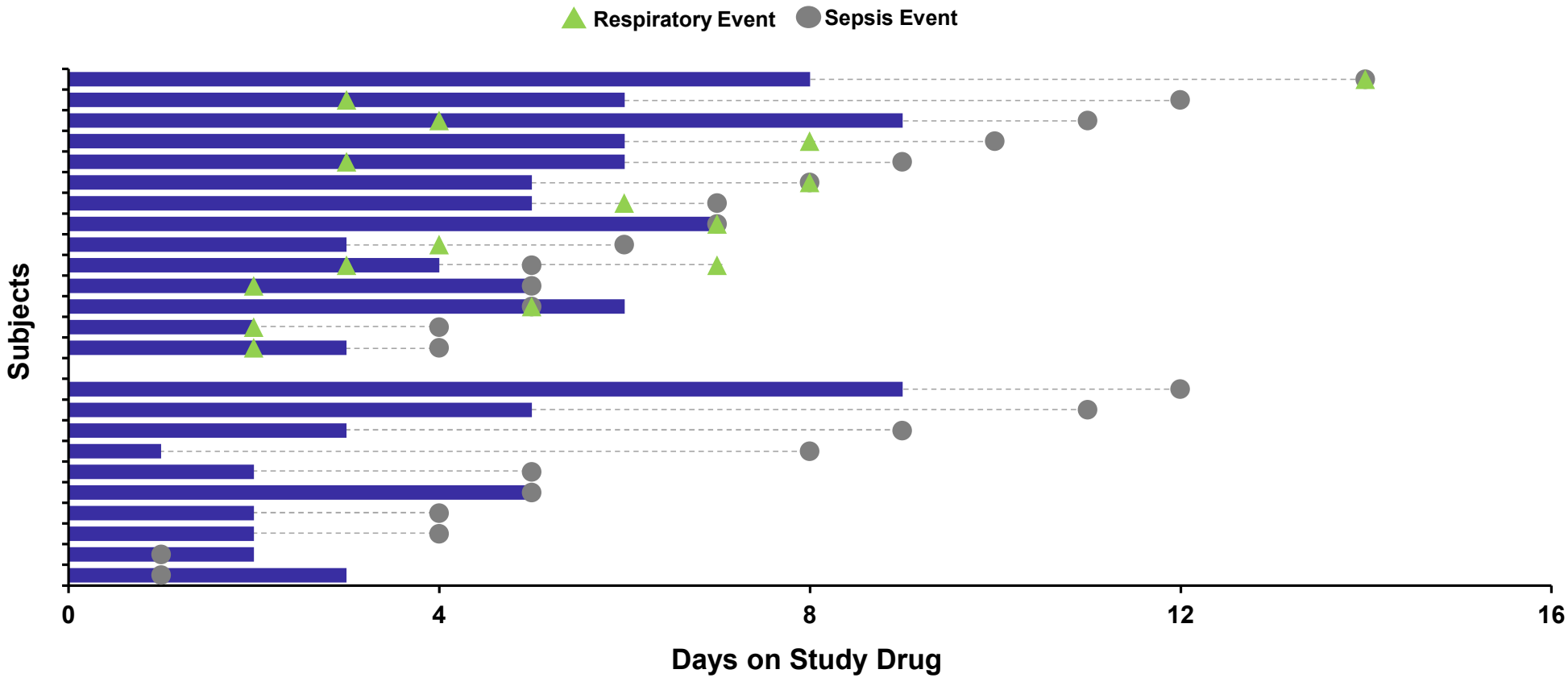
Terlipressin Subjects with Sepsis AE

Integrated Studies (Safety Population)



Sepsis AE includes abdominal sepsis, enterococcal sepsis, klebsiella sepsis, septic shock, sepsis syndrome, sepsis, and urosepsis

Early Sepsis AEs in Terlipressin Subjects and Associated Respiratory AEs
Integrated Studies (Safety Population)



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Summary of Multi-organ Dysfunction Syndrome Events
Integrated Studies (Safety Population)

	Terlipressin N=349 %	Placebo N=249 %
AEs up to 7 days post-treatment	5.4	3.2
Deaths up to 30 days post-treatment	6.3	3.2

Multiple-organ Dysfunction Syndrome Definition

- **Over 50% of subjects with MODS had MODS at Baseline**
  - Did not appear to worsen
- **Evaluation of REVERSE study data**
  - Objective definition for an AE of MODS in this subject population
- **Investigators used CLIF-SOFA scores and ACLF grades**
  - Well-validated scoring systems
  - Used to capture MODS AEs in CONFIRM study

Multiple-organ Dysfunction Syndrome
CONFIRM, OT-0401, and REVERSE Studies

	CONFIRM Study		OT-0401 Study		REVERSE Study	
	Terlipressin N=200 %	Placebo N=99 %	Terlipressin N=56 %	Placebo N=55 %	Terlipressin N=93 %	Placebo N=95 %
AEs	2.5	3.0	7.1	0.0	10.8	5.3
SAEs	4.5	3.0	8.9	0.0	12.9	5.3
Deaths up to 30 days post-treatment	4.5	3.0	8.9	0.0	8.6	5.3

Most Common Ischemic AEs with Onset ≤24 Hours After Last Dose
Integrated Studies (Safety Population)

Preferred Term[1,2]	Terlipressin N=349 %	Placebo N=249 %
Ischemic AEs up to 24 hours after dose	7.2	0.4
Skin discoloration	1.7	0.0
Cyanosis	1.4	0.0
Intestinal ischemia	1.1	0.0
Withdrawals due to ischemia-related AEs	3.7	0.4
Deaths due to ischemia-related AEs	0.0	0.0
Events of skin necrosis	0.0	0.0

1. Subjects were counted only if study drug was received that day.
2. Subjects with multiple AEs of one preferred term are counted once.

Serious Ischemic-related Adverse Events
Integrated Studies (Safety Population)

	Terlipressin N=349 %	Placebo N=249 %
Total subjects with SAEs[1,2]	**2.9**	**0.4**
Intestinal ischemia	**1.1**	**0.0**
Vascular skin disorder	**0.6**	**0.0**
Cyanosis	**0.3**	**0.0**
Livedo reticularis	**0.3**	**0.0**
Myocardial infarction	**0.3**	**0.0**
Poor peripheral circulation	**0.3**	**0.0**
Myocardial ischemia	**0.0**	**0.4**
Deaths	**0.0**	**0.0**

1. Up to 30 days posttreatment
2. Subjects with multiple AEs of one preferred term are counted once.

Ischemic Events

- **Incidence of ischemic events on terlipressin**
  - Integrated Phase 3 studies: 7.2%
  - Literature: 4-13%
- **Manageable with dose interruption**
  - Followed by dose reduction or permanent discontinuation

Gastrointestinal Bleeding Events

CONFIRM (Safety Population)

	Terlipressin N=200 %	Placebo N=99 %
Gastrointestinal disorders	15.0	6.1
Gastrointestinal hemorrhage	4.0	0
Esophageal varices hemorrhage	1.5	2.0
Upper gastrointestinal hemorrhage	1.5	2.0

Safety Conclusions

- AEs are generally predictable, recognizable, and manageable
- Rates of AEs were high in both treatment groups
- Type and severity were consistent with terlipressin and with decompensated cirrhosis
- Respiratory failure was more common in subjects with ACLF grade 3 and respiratory compromise
- Detect and treat infection early
- Ischemia manageable with prompt treatment interruption
- Supports use in HRS-1

Risk Management


Khurram Jamil, MD

Khurram Jamil, MD

Vice President, Clinical Research in Hepatology
Critical Care Division
Mallinckrodt

Risk Management Overview

- Selection of appropriate patients
- Respiratory failure minimization
- Expected impact
- Risk management tools

Selection of Appropriate Patients

- **Use in patients with SCr <5 and ACLF 0-2**
- **Patients with SCr ≥5[1] or ACLF 3**
  - Lower rate of HRS Reversal
  - Higher rate of serious adverse events
  - Higher mortality

1. Highest grade of kidney failure within the Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) score

Mortality With Baseline ACLF 0-2 and 3
Integrated Studies (ITT Population)

	Baseline ACLF 3		Baseline ACLF 0-2	
	Terlipressin N=72 %	Placebo N=49 %	Terlipressin N=280 %	Placebo N=206 %
Death by Day 14	47.2	38.8	19.3	20.4
Death by Day 90	66.7	53.1	43.6	46.6

Mortality With Baseline ACLF 0-2 and 3
Integrated Studies (ITT Population)

	Baseline ACLF 3		Baseline ACLF 0-2	
	Terlipressin N=72 %	Placebo N=49 %	Terlipressin N=280 %	Placebo N=206 %
Death by Day 14	47.2	38.8	19.3	20.4
Death by Day 90	66.7	53.1	43.6	46.6

Mortality With Baseline SCr ≥5 and <5
Integrated Studies (ITT Population)

	Baseline SCr ≥5 mg/dL		Baseline SCr <5 mg/dL	
	Terlipressin N=44 %	Placebo N=33 %	Terlipressin N=308 %	Placebo N=223 %
Death by Day 14	54.5	27.3	20.8	23.3
Death by Day 90	70.5	51.5	45.1	47.5

Mortality With Baseline SCr ≥5 and <5
Integrated Studies (ITT Population)

	Baseline SCr ≥5 mg/dL		Baseline SCr <5 mg/dL	
	Terlipressin N=44 %	Placebo N=33 %	Terlipressin N=308 %	Placebo N=223 %
Death by Day 14	54.5	27.3	20.8	23.3
Death by Day 90	70.5	51.5	45.1	47.5

Risk Identification: Respiratory Events

- **Increased rate of respiratory events**
  - Respiratory failure
  - Deaths in respiratory failure patients
- **Events of sepsis related to respiratory events**
  - Deaths in respiratory-related sepsis patients

Patients at Increased Risk for Respiratory Events

- **Decompensated cirrhosis and ≥3 failing organs at Baseline**
  - ACLF Grade 3
- **Recent history, ongoing, or emergent events**
  - Primarily: dyspnea, pleural effusion, pneumonia, atelectasis, hematemesis and upper GI hemorrhage

Clinical Measures to Mitigate Risk for Respiratory Events Prior to Terlipressin Treatment

- **Hepatic encephalopathy (Grade ≥3) should be treated and the airway should be protected as clinically indicated prior to initiating terlipressin**
- **Do not treat with terlipressin until any pulmonary edema, pneumonia, tachypnea, or dyspnea have been adequately addressed or resolved**

Patient Management to Mitigate Risk for Respiratory Events During Terlipressin Treatment

- **Do not increase dose with cardiorespiratory AEs**
- **Close observation of respiratory status**
- **Patients with fluid overload or respiratory symptoms:**
  - Evaluate for pulmonary edema
  - Consider reduction or discontinuation of albumin and fluids
  - Consider short term diuretic therapy
  - If symptoms persist: reduce, interrupt, or discontinue terlipressin
- **If pneumonia occurs or progresses, or pulmonary edema is severe, or there is new onset or worsening HE ≥3 with risk of aspiration: interrupt or discontinue terlipressin**

CONFIRM Study Protocol Reinforcement Training

Prior to initiating or continuing terlipressin

- Do not treat with terlipressin if a patient has pulmonary edema,

During treatment

- Do not increase dose with cardiorespiratory AEs
- Patients with fluid overload or respiratory symptoms:
  - Consider temporary dose/volume reduction or discontinuation of albumin and fluids
  - Consider short term diuretic therapy
  - If symptoms persist: reduce, interrupt, or discontinue terlipressin

Current Proposed Risk Management

Patients at increased risk for SAEs and death

- **Patients with SCr ≥5 or ACLF 3**
- **Patients at increased risk respiratory failure**
  - **Grade ≥3 hepatic encephalopathy**
  - **Recent history, ongoing, or emergent specific events**

Prior to initiating or continuing terlipressin

- **Hepatic encephalopathy (Grade ≥3) should be treated and the airway should be protected as clinically indicated prior to initiating terlipressin**
- **Do not treat with terlipressin until any** pulmonary edema, **pneumonia, tachypnea, or dyspnea have been adequately addressed or resolved**

During treatment

- Do not increase dose with cardiorespiratory AEs
- Patients with fluid overload or respiratory symptoms:
  - **Evaluate for pulmonary edema**
  - Consider temporary dose/volume reduction or discontinuation of albumin and fluids
  - Consider short term diuretic therapy
  - If symptoms persist: reduce, interrupt, or discontinue terlipressin
- **If pneumonia occurs or progresses, or pulmonary edema is severe, or there is new onset or worsening HE ≥3 with risk of aspiration: interrupt or discontinue terlipressin**

Expected Impact of Proposed Respiratory Risk Mitigation and Use in Appropriate Patients

Respiratory Failure and Sepsis SAEs and Deaths with and without Mitigation
CONFIRM Study (ITT Population)

	Without Mitigation for Respiratory Failure and Appropriate Patients (ACLF 0-2, SCr <5)		With Mitigation for Respiratory Failure and Appropriate Patients (ACLF 0-2, SCr <5)	
	Terlipressin N=200 %	Placebo N=99 %	Terlipressin N=131 %	Placebo N=74 %
Respiratory Failure				
SAEs	14.0	5.1	4.6	6.8
Deaths	12.0	4.0	3.1	5.4
Sepsis				
SAEs	9.0	0.0	6.1	0.0
Deaths	7.5	0.0	4.6	0.0

Respiratory Failure and Sepsis SAEs and Deaths with and without Mitigation
CONFIRM Study (ITT Population)

	Without Mitigation for Respiratory Failure and Appropriate Patients (ACLF 0-2, SCr <5)		With Mitigation for Respiratory Failure and Appropriate Patients (ACLF 0-2, SCr <5)	
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Respiratory Failure and Sepsis SAEs and Deaths with and without Mitigation
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Mortality With and Without Mitigation
CONFIRM and Integrated Studies (Safety Population)

	Without Mitigation for Respiratory Failure and Appropriate Patients (ACLF 0-2, SCr <5)		With Mitigation for Respiratory Failure and Appropriate Patients (ACLF 0-2, SCr <5)	
	Terlipressin %	Placebo %	Terlipressin %	Placebo %
CONFIRM Study	N=199	N=101	N=130	N=75
Death by Day 14	26.6	23.8	14.6	21.3
Death by Day 90	50.3	44.6	39.2	42.7
Integrated Studies	N=349	N=249	N=278	N=218
Death by Day 14	24.9	24.1	13.0	20.7
Death by Day 90	48.1	48.2	37.4	46.4

Mortality With and Without Mitigation
CONFIRM and Integrated Studies (Safety Population)

	Without Mitigation for Respiratory Failure and Appropriate Patients (ACLF 0-2, SCr <5)		With Mitigation for Respiratory Failure and Appropriate Patients (ACLF 0-2, SCr <5)	
	Terlipressin %	Placebo %	Terlipressin %	Placebo %
CONFIRM Study	N=199	N=101	N=130	N=75
Death by Day 14	26.6	23.8	14.6	21.3
Death by Day 90	50.3	44.6	39.2	42.7
Integrated Studies	N=349	N=249	N=278	N=218
Death by Day 14	24.9	24.1	13.0	20.7
Death by Day 90	48.1	48.2	37.4	46.4

Risk Management Tools

- Label
- Education plan
- Limited distribution
- Enhanced pharmacovigilance
- Post-approval Prospective Cohort Safety Study

Proposed Label: Respiratory Failure, SCr ≥5 and ACLF 3

Warnings and Precautions

- **Baseline serum creatinine greater than or equal to 5 and ACLF grade 3**
  - Patients had higher rates of serious adverse events and all-cause mortality and experienced a lower rate of HRS reversal. Use in patients with SCr ≥5 mg/dL and/or ACLF grade 3 should be considered only when the anticipated benefit to the patient outweighs the potential risk
- **Respiratory Failure**
  - Do not administer to patients with new onset or worsening dyspnea, tachypnea, or significant respiratory disease until the patient is stabilized
  - Due to the risk of aspiration, patients with worsening hepatic encephalopathy (Stage ≥3) should be treated and the airway protected as clinically indicated.
  - Closely monitor patients for signs of fluid overload. Manage fluid overload by reducing the administration of albumin and other fluids and judicious use of diuretics

Dosage and administration

- Do not increase the dose in the presence of ongoing significant adverse reactions
- Management of adverse reactions may include temporary dose reduction or interruption. If severe adverse reactions persist following dose adjustment, permanently discontinue

Education Plan

- Direct communication to providers and institutions
- Medical conference training programs
- Field training materials
- Speaker programs
- Webinars
- Digital media
- Product website

Post-approval Prospective Cohort Safety Study

- **Assess terlipressin safety with focus on events of interest**
  - Respiratory failure
  - Sepsis
- **Assess effectiveness of risk management**
  - Selection of appropriate patients
  - Fluid management
  - Clinical management of respiratory conditions
  - Appropriate dosing and dose management
- **Compare to a matched cohort from clinical trial data**

Risk Management Summary

- **Selection of appropriate patients**
  - SCr <5 mg/dL and ACLF <3
- **Respiratory failure mitigation**
  - Respiratory events and mortality
  - Related sepsis events and mortality
- **Expected impact**
  - Reduced events and mortality
  - Improved benefit/risk ratio
- **Risk management tools**
  - Label
  - Education plan
  - Limited distribution
  - Enhanced pharmacovigilance
  - Post-approval Prospective Cohort Safety Study

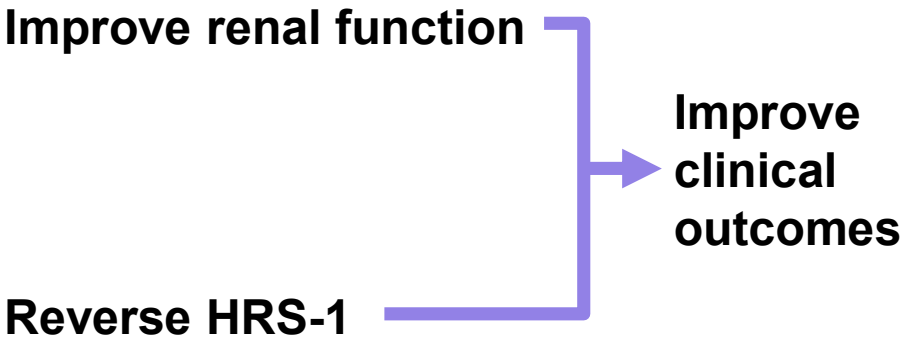
Benefit/Risk and Clinical Considerations


Arun Sanyal, MD

Arun Sanyal, MD

Professor
Department of Internal Medicine
Division of Gastroenterology, Hepatology and Nutrition
Virginia Commonwealth University School of Medicine

HRS-1 Treatment Desired Outcomes



Demonstrated Benefits of Terlipressin

- ✓ **Improve renal function**
- ✓ **Reverse HRS-1**

→ **Improve clinical outcomes**

- ✓ **Less RRT**
  - ✓ Improved RRT-free survival
- ✓ **Facilitate medical management**
- ✓ **Potential to return to compensated state**
- ✓ **Shorter ICU stays**

Liver transplanted patients

- ✓ Less RRT
- ✓ Improved survival

Demonstrated Risks

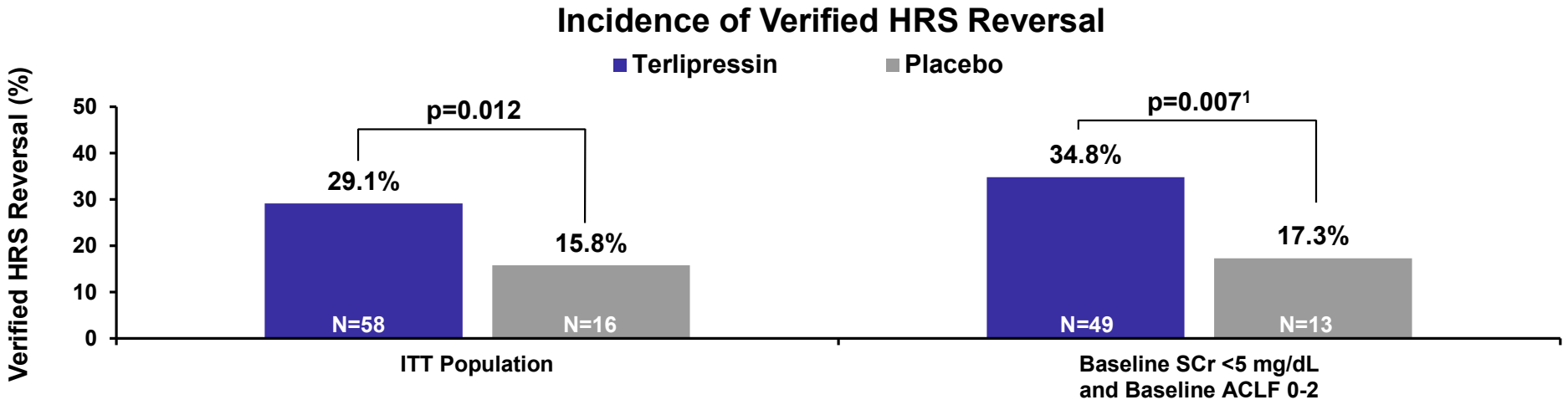
- Respiratory disorders
- Sepsis and septic shock
- Ischemic events
- Gastrointestinal events

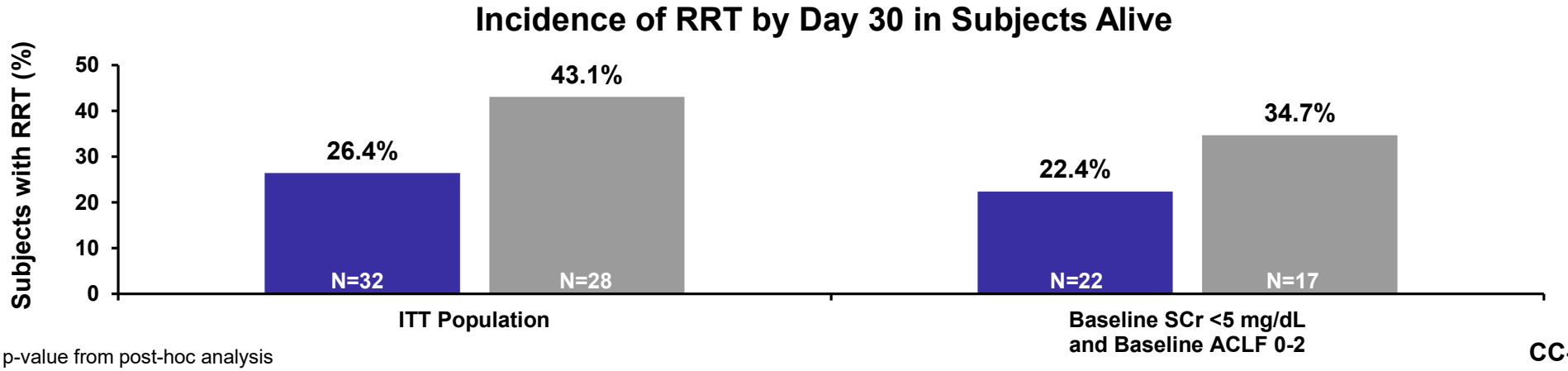
Clinical Perspective on Risk Management

- **Evidence-based strategies from clinical trial data**
- **Optimize benefit/risk for each patient**
- **Avoid treating those with most advanced disease**
  - SCr ≥5 mg/dL or ACLF Grade 3
- **Respiratory failure mitigation fits into routine clinical practice**
  - Protect airway and treat hepatic encephalopathy
  - More aggressive management of fluid balance
  - More aggressive management of respiratory function
  - Stop or avoid terlipressin for florid pulmonary edema or pneumonia

Incidence of Verified HRS Reversal and RRT by Day 30 in Subjects Alive with Baseline SCr <5 mg/dL and Baseline ACLF Grade 0-2

CONFIRM Study





1. Nominal p-value from post-hoc analysis

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Number Needed to Treat/Harm (NNT/NNH)
CONFIRM Study (ITT Population)

	Without Mitigation for Respiratory Failure and Appropriate Patients (ACLF 0-2, SCr <5)	
	NNT	**NNH**
HRS Reversal	**6**	**-**
Alive w/o RRT by Day 90	**21**	**-**
No RRT by Day 30	**10**	**-**
No RRT Post-Transplant	**4**	**-**
Ischemic Event SAEs	**-**	**100**
Respiratory SAEs	**-**	**11**
Sepsis SAEs within 7 Days Post-Treatment	**-**	**25**

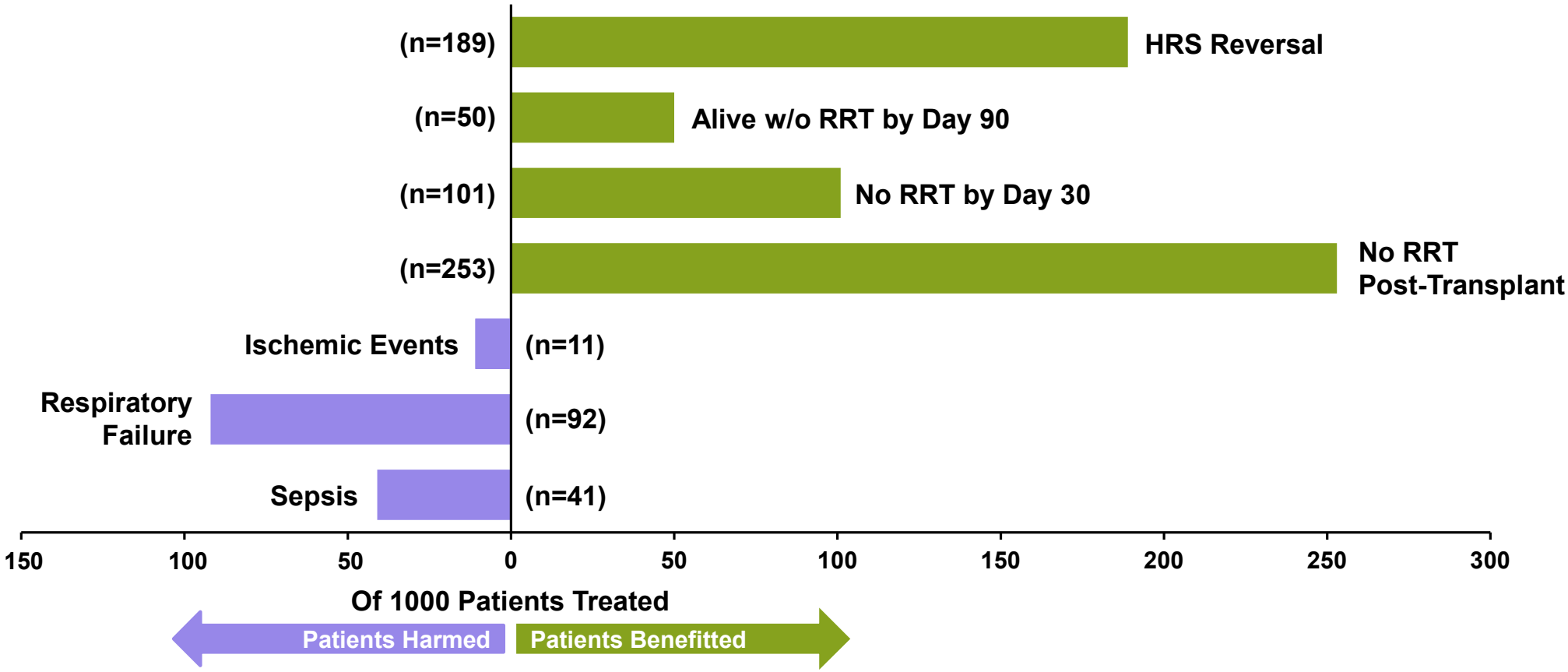
Number Needed to Treat/Harm (NNT/NNH)
CONFIRM Study (ITT Population)

	Without Mitigation for Respiratory Failure and Appropriate Patients (ACLF 0-2, SCr <5)		With Mitigation for Respiratory Failure and Appropriate Patients (ACLF 0-2, SCr <5)	
	NNT	NNH	NNT	NNH
HRS Reversal	6	-	4	-
Alive w/o RRT by Day 90	21	-	12	-
No RRT by Day 30	10	-	11	-
No RRT Post-Transplant	4	-	7	-
Ischemic Event SAEs	-	100	-	130
Respiratory SAEs	-	11	-	N/A[1]
Sepsis SAEs within 7 Days Post-Treatment	-	25	-	44

1. Placebo has higher incidence than terlipressin with mitigation

Additional Benefits and Harms of Terlipressin over Albumin: Without Mitigation for Respiratory Failure and Appropriate Patients (ACLF 0-2, SCr <5)

CONFIRM Study (Derived from NNT / NNH)



AEs of harm: Serious Adverse Events

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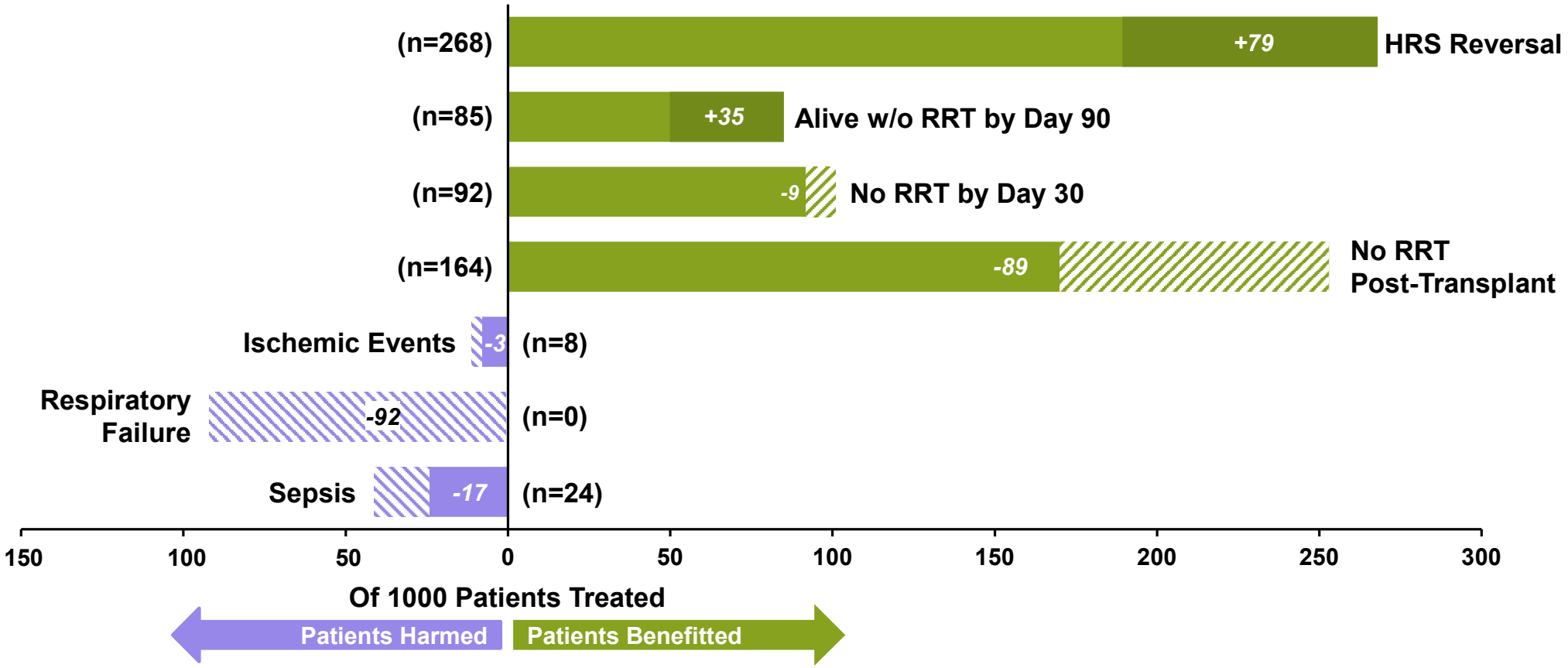
Additional Benefits and Harms of Terlipressin over Albumin: With Mitigation for Respiratory Failure and Appropriate Patients (ACLF 0-2, SCr <5)

CONFIRM Study (Derived from NNT / NNH)



AEs of harm: Serious Adverse Events

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Benefit/Risk Conclusions

- Favorable Benefit/Risk
- Benefits clinically meaningful
- Risks well characterized and generally manageable
- Worldwide standard of care for HRS-1
- Level 1 evidence from 2 positive RCTs supports approval in US
- Urgent need to improve care for these patients